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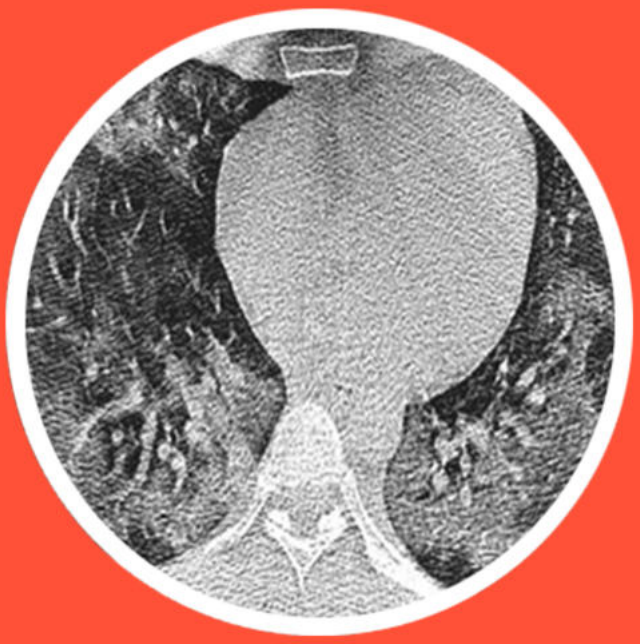
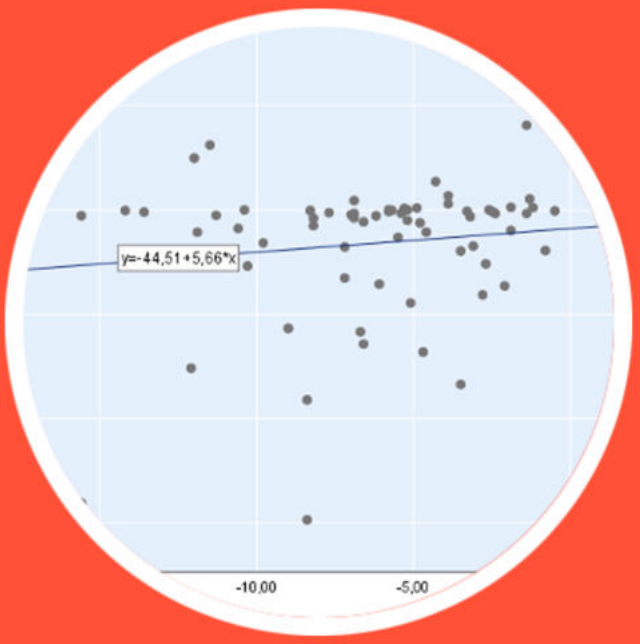
# The European Research Journal







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# The European Research Journal

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## Original Articles

## Case Report

The European Research Journal 2021;7(6):541-549 Original Article

DOI: 10.18621/eurj.855510 *Hematology*

# The infection rate in new diagnosis and relapsed/refractory multiple myeloma patients who had bortezomib-based chemotherapy and relationship between development of infection and lymphocyte/monocyte ratio

**Merve Pamukçuoğlu[1], Nuran Ahu Baysal[2], Mehmet Sezgin Pepeler[1]**

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## ABSTRACT

**Objectives:** Multiple Myeloma (MM) is a disease caused by the clonal proliferation of plasma cells. In recent years, proteozom inhibitors, immunomodulatory agents and monoclonal antibodies have been used in the treatment of MM. In this study, the relation of bortezomib, one of the proteozoma inhibitors used in the treatment of MM, with the development of infection was investigated.

**Methods:** We retrospectively evaluated 56 patients who had MM treated with bortezomib-based regimen. We tried to determine the relationship between infection with immunoglobulin G levels at the time of diagnosis, lymphocyte absolute values at the time of diagnosis, lymphocyte absolute values at the time of chemotherapy, neutrophil absolute value at the time of chemotherapy, lymphocyte absolute values at the time of infection, monocyte absolute value at the time of infection, and the lymphocyte/monocyte (L/M) ratio at the time of infection. The effects of L/M ratio on progression free survival (PFS) and overall survival (OS) were also examined.

**Results:** Thirty (53.6%) of the 56 patients were newly diagnosed, 26 (46.4%) of 56 patients were relapsed/refractory MM. The bortezomib-based regimen was given to all patients. Of the 56 patients included in the study, 21 (37.5%) were female, 35 were male (62.5%). The ages of the patients was 28-79 years (median: 58.5 years). No infection attack was observed in 31 (55.4%) patients. Disease stage (R-ISS) ($p = 0.032$), presence or absence of co-morbid disease ($p = 0.035$), disease status during an infection attack ($p < 0.01$), lymphocytopenia at the time of chemotherapy ($p = 0.003$), absolute value of lymphocytopenia at the time of infection attack ($p < 0.01$) and L/M ratio ($p < 0.01$) had a significant relation with development of infection. Lymphocytopenia at the time of infection attack ($p < 0.01$, OR < 1, 94.6% CI) and L/M ratio ($p < 0.01$, OR < 1, 91.1% CI) had been found significant in univariate logistic regression analysis. Lymphocytopenia at the time of infection attack ($p = 0.002$, OR < 1, 95% CI) and L/M ratio ($p = 0.003$, OR < 1, 95% CI) had been found significant in multivariate logistic regression analysis. L/M ratio had a significant effect on OS ($p < 0.017$) but not on PFS ($p > 0.05$).

**Conclusions:** It was determined that L/M ratio has an effect on OS and it is also an independent factor on the development of infection. OS was decreasing and the risk of developing infection was increasing, when the L/M ratio was low.

**Keywords:** bortezomib, infection, lymphocyte/monocyte ratio

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Muliple Myeloma (MM) is a disease caused by clonal proliferation of plasma cells. It constitutes 10% of hematological cancers. For diagnosis, ≥ 10% clonal bone marrow plasma cells in bone marrow or a biopsy proven plasmacytoma plus evidence of one or more multiple myeloma defining events (MDE) namely CRAB (hypercalcemia, renal failure, anemia, or lytic bone lesions). Plasma cell disorder defined as bone marrow clonal plasmacytosis ≥ 60%, serum involved/uninvolved free light chain (FLC) ratio ≥ 100 (provided involved FLC is ≥ 100 mg/L), or > 1 focal lesion on magnetic resonance imaging (MRI) [1].

Many chemotherapeutic agents are used in the treatment of MM. The use of melphalan in the treatment of MM was a revolution in the 1950s [2], and then the demonstration of the effect of high-dose melphalan and autologous stem cell transplantation on progression-free survival changed the standard treatment approaches in MM [3] In the last 10 years, immunomodulatory drugs such as Thalidomide, Lenalidomide, Pomalidomid (IMID) and proteasome inhibitors such as Bortezomib have been started to use [4, 5]. Subsequently, CD38-targeted monoclonal antibody 'Daratumumab' was added in the MM patients' treatment [6]. Bortezomib is still being the first treatment option in MM in Turkey.

With the use of high-dose melphalan and bortezomib and new agents in the IMID group, there was a dramatic change in the mean survival in MM patients. Overall survival had been extended from 3 years to 8-10 years. This increase in efficacy also led to changes in the spectrum of side effects. Humoral immunodeficiency has been usually seen in MM patients. After using these drugs in the MM patients' treatment, they began to affect cellular immune functions, and changing infectious complication processes were begun [7, 8].

Bortezomib is a molecule that reversibly and selectively inhibits the 26S proteasome and shows its effect through nuclear factor-kB (NF-kB) [7, 9-11]. It causes apoptosis by inhibition of NF-kB. It also performs T cell suppression through the same mechanism. Therefore, T cells containing high levels of NF-kB are more sensitive to bortezomib treatment. $CD4^+$ T cells affected by bortezomib treatment produce less IFN-gamma and IL-2 [10]. This explains the anti-inflammatory and immunomodulatory effect of bortezomib [7].

Hematological side effects occur due to the anti-inflammatory and immunomodulating effects of bortezomib. The most important of these are neutropenia and thrombocytopenia [7]. Monocytopenia and lymphocytopenia (T-cell suppression) associated with bortezomib treatment may also occur [8, 9].

In this study, it is aimed to reveal the relationship between infection development with variables such as absolute lymphocyte value, lymphocyte/monocyte ratio (L/M), and IgG level in newly diagnosed and relapsed/refractor MM patients who had treated with bortezomib-based chemotherapy. At the same time, the L/M ratio and overall survival relationship had been determined.

## METHODS

We retrospectively evaluated 56 patients who had MM treated with bortezomib based regimen. Type of Infection were determined. Lymphocyte absolute values at the time of diagnosis, immunoglobulin G levels at the time of diagnosis, lymphocyte absolute values at the time of chemotherapy, neutrophil value at the time of chemotherapy, lymphocyte absolute values at the time of infection, and monocyte absolute value at the time of infection were recorded from the file information. The L/M ratio of the patients at the time of infection were calculated and transferred to the SPSS database. We tried to determine the relationship between infection with immunoglobulin G levels at the time of diagnosis, lymphocyte absolute values at the time of diagnosis, lymphocyte absolute values at the time of chemotherapy, lymphocyte absolute values at the time of infection, monocyte absolute value at the time of infection, and the L/M ratio at the time of infection. The effects of L/M ratio on progression free survival (PFS) and overall survival (OS) were also examined.

Gazi University Faculty of Medicine ethical committee has approved this study on 12/09/2014 with the number of 25901600-3086.

### Determinations

International staging system (ISS):

- Stage-I: serum beta - 2 microglobulin level < 3.5 mg/dl and serum albumin level ≥ 3.5 g/dl
- Stage-II: out of ISS stage I and stage III criteria

- Stage-III: serum beta-2 microglobulin level ≥ 5.5 mg/L [12].

### Revised International Staging System (R-ISS):

- R-ISS I: serum β2-microglobulin level < 3.5 mg/L, serum albumin level ≥ 3.5 g/dL, no high-risk cytogenetic anomaly (CA) [del(17p) and/or t(4;14) and/or t(14;16)], and normal LDH level (less than the upper limit of normal range)

- R-ISS II : out of ISS stage I and stage III criteria

- R-ISS III: serum β2-microglobulin level > 5.5 mg/L and high-risk CA or high LDH level [13].

**Table 1. Patients' MM subtypes, M protein level, ISS and R-ISS stages and Co-morbidity at the diagnosis**

| | Number of the patients | % |
|---|---|---|
| **MM subtypes** | | |
| IgG kappa | 24 | 42.9 |
| IgG lambda | 13 | 23.2 |
| Ig A kappa | 3 | 5.4 |
| Ig A lambda | 4 | 7.1 |
| Ig D lambda | 3 | 5.4 |
| kappa light chain | 4 | 7.1 |
| lambda light chain | 4 | 7.1 |
| non-secretory | 1 | 1.8 |
| **M protein level** | | |
| < 3 g/dl | 13 | 23.2 |
| >3g/dl | 43 | 76.8 |
| **ISS stage** | | |
| stage-1 | | 21.4 |
| stage-2 | 10 | 17.9 |
| stage-3 | 34 | 60.7 |
| **R-ISS stage** | | |
| stage-1 | 10 | 17.9 |
| stage-2 | 29 | 51.8 |
| stage-3 | 17 | 30.4 |
| **Co-morbidity** | | |
| no co-morbidity | 22 | 39.3 |
| DM | 9 | 16.1 |
| CRF | 10 | 17.9 |
| HT | 9 | 16.1 |
| AHD | 3 | 5.4 |
| COPD | 1 | 1.8 |
| HF | 1 | 1.8 |
| ARF+SM+COPD+HT | 1 | 1.8 |

MM = multple myeloma, ISS = international scoring system, R-ISS = revised international scoring system, DM = diabetes mellitus, CRF = chronic renal failure, HT = hypertension, AHD = atherosclerotic heart disease, COPD = chronic obstructive pulmonary disease, HF = heart failure, ARF = acute renal failure, SM = secondary malignancy

### Statistical Analysis

Descriptive statistics were presented as mean ± standard deviation and median (minimum-maximum) for numerical variables, and as percentages for categorical variables. The normal distribution of parametric values was determined by the Shapiro-Wilk Test. For determining the significance In statistical analysis, the T-test was used for parametric variables, Mann Whitney U test was used for non-parametric variables. Pearson Chi-Square Test was used to comparing two categorical variables. Univariate and multivariate logistic regression analyzes were performed for advanced statistical analysis. Log-Rank test was used to calculate survival analysis. All statistical evaluations were made using the Statistical Package for Social Sciences (SPSS) for Windows 16 (IBM SPSS Inc., Chicago, IL) program. Statistical significance p-value was accepted as < 0.05 in all analyzes.

## RESULTS

Of the 56 patients included in the study, 21 (37.5%) were females and 35 (62.5%) were males. The median age of the patients was 58.5 years (min-max: 28-79 years). Thirty (53.6%) of 56 patients were newly diagnosed, 26 (46.4%) of 56 patients were relapsed/refractor MM. Table 1 show the patients' MM subtypes, M protein level, ISS and R-ISS stages and co-morbidity at the time of diagnosis. The bortezomib-based regimen was given to all patients. Accordingly, 43 (76.8%) patients had bortezomib 1.3 mg/m2 sc (1, 8, 15, and 22 days), cyclophosphamide 300 mg/m2 PO (1, 8, 15, and 22 days) and dexamethasone 40 mg (1, 8, 15, and 22 days) (VCD) regimen, 13 patients (23.2%) had bortezomib 1.3 mg/m$^2$ sc (Days 1, 8, 15, and 22), melphalan 9 mg/m2 PO, (1-4 Days) and prednisone 60 mg/m$^2$ PO, (Days 1-4) (VMP) chemotherapy regimen.

Thirty-one (55.4%) patient did not have any infection. Pulmonary infection was seen in 17 (30.4%) patients, urinary system infection was seen in 3 (5.4%) patients, lung and urinary system infection was seen in 2 (3.6%) patients, cellulitis was seen in 1 (1.8%) patient, psoas abscess was seen in 1 (1.8%) patient, the unknown origin of fever was seen in 1 (1.8%) patient. Twelve (21.4%) of the patients had an infection in the first cycle, others had an infection in the second or more cycles. Infection agents could be isolated in only 7 (12.5%) patients. Accordingly: E. Coli infection was seen in 5 (8.9%) patients, viral infection was seen in 1 (1.8%) patient, and coagulase-negative staphylococcal infection was seen in 1 (1.8%) patient. While the patients received bortezomib-based chemotherapy, the median neutrophil values was 0 /mcL (min-max: 0-4000/ mcL). In 8 (14.3%) patients; neutrophil level was ≤ 1000 /mcL, and in 48 (85.7%) patients; neutrophil level was > 1000 /mcL. Before starting chemotherapy, median basal lymphocyte absolute values was 14051/ mcL (min-max: 320-3190 /mcL). The median lymphocyte values measured while receiving chemotherapy was 636/mcL (min-max: 32-1890 mcL ). The median lymphocyte absolute values of the patients in the infection attack was 1775/mcL (min-max: 30-4000/mcL). In twenty (35.7%) patients; lymphocyte values was ≤1000/mcL, in 36 patients (64.3%) lymphocyte values was >1000/mcL. The median monocyte absolute values of the patients in the infection attack was 434/mcL (min-max: 80-1000/mcL). The median IgG value at diagnosis was 3000 mg/dl

**Table 2. Value of age, median level of Ig G level at diagnosis, lymphocytopenia at the time of chemotherapy and L/M ratio**

| | Infection negative | Infection positive | *p* value |
|---|---|---|---|
| Age | 55.87±11.0 | 61.6±112.2 | 0.07t |
| Ig G level at diagnosis | 3325 ( 305-10800) | 3000 (141-13800) | 0.93MU |
| Lymphocytopenia at the time of chemotherapy | 780 (50-1890) | 300 (32-1780) | 0.003MU |
| L/M ratio | 4.6 (1.5-45) | 0.88 (0.04-5) | 0.00MU |

Data are shown as mean ± standard deviation or median (min-max). L/M = lymphocyte/monosyte
T-test, MU: Mann Whitney U test

**Table 3. Variables that are found to be statistically significant/not statistically significant**

| | Infection negative | Infection positive | p value |
|---|---|---|---|
| Gender, n (%) | | | |
| Female | 12 (38.7) | 9 (36) | 0.83x2 |
| Male | 19 (61.3) | 16 (64) | |
| Total | 31 (100) | 25 (100) | |
| Subtypes of MM, n (%) | | | |
| Ig G kappa | 15 (48.4) | 9 (36) | 0.35x2 |
| Others | 16 (51.6) | 16 (64) | |
| Total | 31 (100) | 25 (100) | |
| ISS, n (%) | | | |
| Stage-I | 8 (25.8) | 4 (16) | 0.29x2 |
| Stage -II | 7 (22.6) | 3 (12) | |
| Stage -III | 16 (51.6) | 18 (72) | |
| Total | 31 (100) | 25 (100) | |
| R-ISS, n (%) | | | |
| Stage -I | 6 (19.4) | 4 (16) | 0.032 x2 |
| Stage-II | 20 (64.5) | 9 (36) | |
| Stage-III | 5 (16.1) | 12 (48) | |
| Total | 31 (100) | 25 (100) | |
| Co-morbidity, n (%) | | | |
| No | 16 (51.6) | 6 (24) | 0.035 x2 |
| Yes | 15 (48.4) | 19 (76) | |
| Total | 31 (100) | 25 (100) | |
| Diesea state, n (%) | | | |
| CR | 31 (100) | 1 (4) | < 0.01 x2 |
| Others | 0 | 24 (96) | |
| Total | 31 (100) | 25 (100) | |
| Levelof M protein, n (%) | | | |
| < 3gr/dl | 9 (29) | 4 (16) | 0.25x2 |
| > 3 gr/dl | 22 (71) | 21 (84) | |
| Total | 31 (100) | 25 (100) | |
| Level of creatinin | | | |
| < 2mg/dl | 22 (71) | 14 (56) | 0.24x2 |
| > 2 mg/dl | 9 (29) | 11 (44) | |
| Total | 31 (100) | 25 (100) | |
| Typeofchemotherapy | | | |
| VCD | 25 (80.6) | 18 (72) | 0.44x2 |
| VMP | 6 (19.4) | 7 (28) | |
| Total | 31 (100) | 25 (100) | |
| Number of Bortezomib cycles | | | |
| ≤ 4 cycle | 27 (87.1) | 21 (88) | 0.53x2 |
| > 4 cycle | 4 (12.9) | 4 (12) | |
| Total | 31 (100) | 25 (100) | |
| Neutropenia | | | |
| < 1000 | 2 (6.5) | 6 (24) | 0.06x2 |
| > 1000 | 29 (93.5) | 19 (76) | |
| Total | 31 (100) | 25 (100) | |
| Lymphocytopenia | | | |
| < 1000 | 0 | 20 (80) | < 0.01 x2 |
| > 1000 | 31 (100) | 5 (20) | |
| Total | 31 (100) | 25 (100) | |

L/M = lymphocyte/monosyte, ISS = international scoring system, R-ISS = revised- international scoring system, VCD = bortezomib, cyclophosphamide, dexamethasone, VMP =bortezomib, melphalan, prednisolone, x2: chi-quare test

**Table 4. Univariate and multivariate analysis of variables**

| | UNIVARIATE ANALYSIS | | | MULTIVARIATE ANALYSIS | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | p value | OR | 95% CI | *p* value |
| Co-morbidity | 3.37 | 1.06-10.7 | 0.039 | 0.4 | 0.17-1.29 | 0.146 |
| Diseade State | 0.99 | 0.99-1 | < 0.01 | 3.6 | 0-1 | 0.95 |
| Lymphocytopenia at the time of chemotherapy | 0.99 | 0.99-1 | 0.018 | 0.96 | 0.06-15 | 0.99 |
| Lymphocytopenia | 0.99 | 0.994-0.998 | < 0.01 | 0.99 | 0.99-1 | 0.002 |
| L/M ratio | 0.173 | 0.065-0.45 | < 0.01 | 0.007 | 055-0.88 | 0.003 |

L/M = lymphocyte/monosyte, CI = confidental interval, OR = odss ratio

(min-max: 141-13800 mg/dl). The median value of L/M ratio was 2.00 (min-max: 0.04-45).

A statistically significant correlation was seen in disease stage (R-ISS) ($p = 0.032$), presence or absence of co-morbid disease ($p = 0.035$), disease status during an infectious attack ($p < 0.01$), lymphocytopenia at the time of chemotherapy ($p = 0.003$), absolute value of lymphocytopenia at the time of infection ($p < 0.01$) and the L/M ratio ($p < 0.01$) with the development of infection. According to the R-ISS, patients who had stage 3 and in the presence of co-morbid disease had a higher infection risk while the infection rates were low in patients who had a complete response. Lymphocytopenia was related to the development of infection. Especially, patients who had ≤ 1000 /mcL ($p < 0.01$) lymphocyte level and who had a low L/M ratio (< 2) had a high risk of development of infection. Variables that are found to be statistically significant (or not statistically significant) relation with development of infection are shown in Table 2 and Table 3.

Disease status during infection ($p < 0.01$, OR<1, 98.2% CI), lymphocytopenia at the time of infection ($p < 0.01$, OR < 1, 94.6% CI) and L/M ratio ($p < 0.01$, OR < 1, 91.1% CI) were significant in univariate logistic regression analysis. Infection rate was lower in patients with complete response. Accordingly, infection rates increase in patients who had lymphocytopenia and in patients who had a low level of L/M ratio. Significant parameters in univariate analysis were re-evaluated in multivariate logistic regression analysis, lymphocytopenia at the time of infection and L/M ratio were found significant (respectively: $p = 0.002$, OR < 1, 95% CI; $p = 0.003$, OR < 1, 95% CI). The variables that are significant in univariate and multivariate analysis are shown in Table 4.

When the effects of the independent variable of L/M ratio on PFS and OS were examined; L/M ratio had no significant effect on PFS ($p > 0.05$), while had a significant effect on OS ($p < 0.017$). The mean OS was 33 ± 2.7 months (min-max: 27.53-38.47 months). The cut-off value of the L/M ratio was 2 (this is the median value of the L/M ratio). Mean OS survival of patients who had L/M ≥ 2 was 37 ± 2.5 months (min-max: 32- 41.96 months), mean OS of patients who had L/M < 2 was 28 ± 3.2 months (min-max: 21.7-34.27/ months). Fig. 1 show relationships between the OS and the L/M ratio.

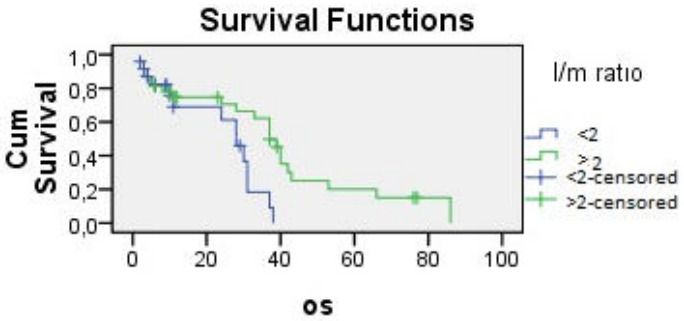


**Fig. 1. Relationship between lymphocyte/monosyte (L/M) ratio and survival.**

## DISCUSSION

It has been reported in the literature that the frequency of viral infections is high in MM patient who had a bortezomib therapy. Especially, it has been emphasized that there is a relationship between bortezomib and Herpes Zoster infection [10, 11, 14]. As we have been stated, the relationship between bortezomib and infection development is due to the lymphocytopenia-inducing effect of bortezomib [6]. The result we obtained in this study also supports these findings. It has been shown that lymphocytopenia and the decrease in the L/M ratio are independent variables on

the development of infection. We also find that R-ISS, co-morbidity, disease state have significant affect on development of infection in MM patients, however, were not found an independent factors.

Pang *et al*. [15] claimed that neutrophile+monocyte/lymphocyte ratio (NMLR) is an independent variable on progression-free survival. Newly diagnosed patients who received VCD chemotherapy regimen were included in this study. The NMLR ratio was calculated for each patient and a value of 1.9 was taken as the cut-off value. It has been shown that immune restructuring is more effective and disease exacerbation is less in patients who had a NMLR < 1.9. On the other hand, it is known that the microenvironment is important in the course of the disease in MM patients. Neutrophils, lymphocytes and monocytes are being in this microenvironment [16, 17]. In some studies, it has been shown that the ratio of absolute neutrophil value to absolute lymphocyte value and the ratio of absolute lymphocyte value to absolute monocyte value are effective in immune remodeling in MM patients, and this affects progression-free survival [16, 18, 19]. It is also emphasized that the cells that are particularly effective in the microenvironment of MM are neutrophils and monocytes, and the treatment options may change according to the neutrophil lymphocyte ratio and the lymphocyte-monocyte ratio in patients with MM [20]. In recent years, the use of immunomodulatory drugs and the use of CAR-T cell therapy, especially in patients with relapsed / refractory MM, have shown the importance of immune abnormality in the course of the disease in patients with MM. In vivo balance to be established in the immune environment affects the course of the disease [21].

It has been shown that absolute neutrophil value, absolute lymphocyte value, and absolute monocyte value and their ratio to each other are independent variables in solid tumors and hematological cancers and in the course of the disease after autologous stem cell transplantation [22-26]. In most of these studies, it was shown that high neutrophil/lymphocyte ratio and low lymphocyte/monocyte ratio were associated with poor prognosis. On the contrary, there are studies in the literature that showing the neutrophil/lymphocyte ratio is not effective on survival [19]. Romena *et al*. [20], showed that the monocyte ratio is effective on the microenvironment in myeloma bone marrow. Especially, it is emphasized that it enables growth in myeloma cells. When all these are taken into consideration, it is emphasized that neutrophil, lymphocyte and monocytes and especially NMLR parameter are effective on survival in MM patients. The reason for better progression-free survival in patients with a low NMLR rate may be due to the low monocyte ratio that enables the growth of the myeloma cell. There are also studies claiming that the increase in the L/M ratio is associated with a good prognosis [26] It is still unknown how the changes in lymphocyte and monocyte ratio affect the risk of infection. However, absolute lymphocyte value, absolute monocyte value and L/M ratio are closely related to the immune system [27]. It is also known that alloreactive T lymphocytes are suppressed, especially in bortezomib-based regimens [10]. As a result of all these, it can be said that absolute lymphocyte and monocyte values and L/M ratio might be occurred predisposition for infections. It is also known that bortezomib prevents the growth of myeloma cells with causing to monocytopenia.

Decreasing in the L/M ratio, in other words, higher monocyte value relative to lymphocyte value, might be associated with infection in bortezomib-based regimens. If bortezomib-based regimen is used in relapsed refractory cases or newly diagnosed cases of MM, lymphocytopenia should be tried to prevent. On the other hand, it is necessary to keep the monocyte value at certain rates in order to prevent tumor growth. Yang *et al*. [27], examined the relationship between L/M ratio and OS. The median L/M ratio in our study is the 2. Overall survival was longer in patients who had L/M ratio ≥ 2.

## CONCLUSION

It was determined that L/M ratio has an effect on OS and it is also an independent factor on the development of infection. OS was decreasing and the risk of developing infection was increasing, when the L/M ratio was low. We have to say that; there is some restriction in this study such as number of patients and power effect of lymphocytopenia in multivariate analysis. Therefore; more studies which are including more patients, are needed for claiming the lymphocytopenia and L/M ratio are an independent variable on the development of infection and L/M ratio has an effect on OS. After then, L/M will be a follow-up pa-

rameter in the development of infection in bortezomib-based regimens and it will be considered as an effective parameter on OS.

*Authors' Contribution*

Study Conception: MP, NAB, MSP; Study Design: MP, NAB, MSP; Supervision: MP, NAB, MSP; Funding: MP, NAB, MSP; Materials: MP, NAB, MSP; Data Collection and/or Processing: MP, NAB, MSP; Statistical Analysis and/or Data Interpretation: MP, NAB, MSP; Literature Review: MP, NAB, MSP; Manuscript Preparation: MP, NAB, MSP and Critical Review: MP, NAB, MSP.

*Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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# Turkish adaptation of the undergraduate nursing clinical evaluation form: a validity and reliability study

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## ABSTRACT

**Objectives:** The study was conducted for the purpose of determining the validity and reliability of the "Undergraduate Nursing Clinical Evaluation Form (CEF)" in a Turkish sample.

**Methods:** One hundred sixty-seven students enrolled in Faculty of Health Sciences Department of Nursing participated in the study. Study data were collected via the Student Description Form and CEF. The Cronbach's α internal consistency coefficient was calculated for the reliability of the total scale. Pearson correlation analysis was used to determine the correlation between items and total scores.

**Results:** In the validity of the scale, CFA was used to investigate the consistency of the scale with the original scale. When the fit indices of the model tested using CFA were examined, it was seen that the chi-square value was significant. When the Cronbach's α reliability coefficients were examined, the reliability of the form was found to be quite good in terms of domains and total score. The correlations between the items and total scale score ranged between 0.42 and 0.77. Cronbach's α coefficient was greater than 0.90 for each item.

**Conclusions:** Undergraduate Nursing Clinical Evaluation Form is a valid and reliable tool that can be used in the Turkish culture.

**Keywords:** Nursing, clinical evaluation, validity, reliability

Theoretical knowledge and clinical teaching are inseparable parts of nursing education as in the education programs of all practice-based disciplines [1, 2]. Students gain professional confidence in the fields where clinical teaching is applied. Clinical practice provides students the opportunity to integrate the theoretical knowledge and practice taught in the school by experiencing and practicing in a real environment. It also allows students to use their knowledge in a real-world environment, develop their psychomotor skills, and improve professional relationships [3, 4]. In clinical practice, students have the opportunity to practice what they learn and to see role models that prepare them for the future. At the same time, they develop critical thinking and problem-solving skills and receive the opportunity to see the relationships between health team members [4-7].

Factors such as the type of clinical setting, attitudes, and the experiences of the instructor are important in shaping the clinical experience of students [8]. Relevant studies have focused on identifying students' current and previous clinical practice experiences, and their perceptions of the clinical training process [1, 9, 10-12]. In the study conducted by Chan [13], it was

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reported that clinical practice environments could not provide a positive learning environment for students. In the study conducted by Papathanasiou *et al*. [14] in order to evaluate nursing students' perceptions of clinical learning environments, it was determined that there was a significant gap between the students' expectations of the clinical learning environment and the reality. As a result of the study, it was recommended that the education framework be reorganized. In another study, it was stated that instructors and nurses in the clinic play a particularly important role in integrating nursing students into the clinical environment during clinical practice [15]. In a qualitative study conducted by Serçekuş and Başkale [16] in Turkey, it was determined that nursing students were negatively affected if feedback was given by instructors in front of patients. In the study conducted by Arkan *et al*. [17], it was emphasized that the most significant factor in students' clinical learning was the attitude of instructors.

During clinical practices, the psychomotor skills students have acquired previously are evaluated alongside their cognitive and affective capacities [18]. The evaluation of students during clinical practice is one of the main focuses of nursing education, in order to ascertain that clinical learning goals have been met. Evaluation is an inseparable part of education and is a dynamic process that aims to ensure students learn and develop [19, 20]. On the other hand, students are also expected to give feedback about their experiences after the clinical practice. It is very important for the evaluation process that educators be provided with feedback that adequately represents the views of the students because health care organizations require student feedback to shape educational programs and activities for personal development [8].

There are limited evaluation tools that nursing students can use to provide feedback at the end of clinical practice. In addition, it has been reported that some tools available are problematic in terms of their ability to provide correct evaluation, since they are hard to understand and there are too many deficiencies in the open-ended question format [21, 22]. Therefore, there is a need to develop a tool that can provide feedback which helps instructors to provide a successful clinical practice environment. It was determined in the literature review that there is no evaluation tool that nursing students in Turkey can use to give feedback about their clinical practice. It is thought that the use of a measurement tool in which nursing students evaluate the current state of clinical practice in all its aspects will contribute to identify and solve problems in clinical training.

This study was thus conducted to test the Turkish validity and reliability of the Undergraduate Nursing Clinical Evaluation Form (CEF) developed by Porter *et al*. [8].

### Research Questions

Is the Undergraduate Nursing Clinical Evaluation Form (CEF) for nursing students valid and reliable?

## METHODS

The study was conducted methodologically with nursing students between December 2018 and January 2019.

The sample of the research consisted of second, third and fourth-year students at the Nursing Department of the Faculty of Health Sciences at Bursa Uludag University at the end of the fall semester of the 2018-2019 academic year. Among the students included in the sample, second-year students had completed internal medicine nursing internship practices; third-year students had completed obstetrics and gynecology nursing internship practices; and fourth-year students had completed public health nursing, psychiatric nursing, and surgical diseases nursing internship practices. First-year nursing students were excluded from the research since they had not yet had clinical practice experience at the time of the study.

In the literature, three rules are mentioned for the determination of the sample size in validity and reliability studies. It is emphasized that at least five people should be included per item in order to perform factor analysis. Itis recommended that there be 10 people per item if there is no problem in reaching the sample [23]. If there is a serious limitation in sampling it is recommended that the size of the sample be at least 100 people. Ten students were included per item in order to perform the validity and reliability study of the 30-item CEF, and the size of the sample was calculated as 210 students. Two hundred twenty students who met the research criteria were included in the sample. However, 53 students were excluded from the sample

since they did not fully complete the form and analyses were performed on 167 students. The percentage of the sample reached was 75%.

### Data Collection Tools

The data of the research were collected using the Student Introduction Form and the CEF.

### Student Introduction Form

This form includes questions about the age, gender, year-of-study, and clinical practice fields of the students.

### Undergraduate Nursing Clinical Evaluation Form (CEF)

This was developed by Porter *et al*. [8] in 2011. It is an evaluation tool that can be used by nursing students to provide feedback at the end of the clinical practice process. The form consists of 21 items and five domains. The domains are "Orientation", "Clinical Educator/Teacher", "Ward Staff and Environment", "Clinical Hurdles" and "University". The form has a 5-point Likert type (1 = never, 2 = rarely, 3 = sometimes, 4 = often, 5 = always). The lowest score that can be obtained from the form is 21 and the highest score is 105. The Cronbach's α value of the form is 0.90 [8].

### Data Collection

#### *1. Language Validity*

For language validity, the form was translated from English to Turkish independently by three Turkish linguistic scientists. Afterward, the researchers evaluated the most appropriate translation for each item and prepared a common Turkish text. The scale, which was translated into Turkish, was retranslated to English by two linguistic scientists who were fluent in both Turkish and English and the translated form was compared with the original form. Inappropriate statements were revised to ensure language validity.

#### *2. Content Validity*

After language validity had been ascertained, the draft form was presented to 10 experts in psychiatry, internal medicine, surgery, nursing principles, pediatric nursing, and nursing management to obtain their opinions. The experts were asked to evaluate the draft form in terms of both language and content. The experts scored each item as follows: "4" if an item did not need to be changed; "3" if a minor change was recommended; "2" if a major change was recommended; and "1" if it was recommended that an item be removed for being inappropriate.

#### 3. Application Process

The draft scale developed was given nursing students who were not included in the sample for a pilot application and its intelligibility and the application process were evaluated.

#### *4. Construct Validity*

Confirmatory Factor Analysis (CFA) was used to validate the factors present in the original form of the scale for construct validity. Prior to the analysis, the data set was examined and missing data, extreme values, and normality were checked. The data were analyzed using the lavaan 0.6-3 package in the CFA RStudio Desktop 1.2.1335 for the construct validity of the scale.

#### *5. Determination of Reliability*

To determine the reliability of the CEF, which was developed by Porter *et al*. and consists of 21 items and 5 domains (orientation, clinical educator/teacher, ward staff and environment, clinical hurdles, and university), the Cronbach's α reliability coefficients were calculated from among the internal consistency methods and item-total score analyses were performed.

The students were asked to fill out the questionnaire given by the researchers. Care was taken that the time taken to complete questionnaires did not interfere with students' lecture hours. The maximum length of time it took for students to complete the form was calculated to be 15 minutes. The completed questionnaires were collected and evaluated.

### Ethical Consideration

Written permission was obtained by email from the corresponding author Joanne Porter, who developed the form, in order to use the CEF in the research. Written permission was obtained from the Health Sciences Research and Publication Ethics Committee of Bursa Uludag University (Decision No: 2018-06). Students who agreed to participate in the research were informed that all of the data would be used for scientific purposes and that their answers would not affect

their course marks in any way. Their informed consent was then obtained.

### Statistical Analysis

Statistical analysis of the data was performed in the SPSS 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) statistics package program. The demographic data of the students were presented as frequency and percentage for qualitative variables and mean and standard deviation for qualitative variables. The Cronbach's α internal consistency coefficient was calculated for the reliability of the total scale and five domains. Pearson correlation analysis was used to determine the correlation between items and total scores. In the validity of the scale, CFA was used to investigate the consistency of the scale with the original scale. Prior to the analysis, the data set was examined and missing data, extreme values, and normality were checked. The data were analyzed using the lavaan 0.6-3 package in the CFA RStudio Desktop 1.2.1335 for the construct validity of the scale. In the interpretation of the CFA result, the ratios of the chi-squared value to the degree of freedom, CFI, RMSEA, and SRMR fit indices were used. The significance level was accepted as $\alpha = 0.05$.

## RESULTS

The sociodemographic characteristics of the nursing students included in the study are given in Table 1. When the students evaluated their clinical practice with the CEF, it was determined that the highest score was in the "clinical educator/teacher" domain and the lowest score was in the "ward staff and environment" domain (Table 2).

### Construct Validity of Undergraduate Nursing Clinical Evaluation Form (CEF)

When the fit indices of the model tested using CFA were examined, it was seen that the chi-square value was significant ($\chi2 = 370.543$; $p < 0.001$). Fit indices and acceptable values obtained in the study are given in Table 3. According to these results, it was determined that the $\chi2$/sd, CFI, SRMR, and RMSEA values were within the acceptable limits and that the study provided construct validity.

**Table 1. Sociodemographic characteristics of students**

| Characteristics | n | % |
|---|---|---|
| Year | | |
| Second | 77 | 46.1 |
| Third | 57 | 34.1 |
| Fourth | 33 | 19.8 |
| Age | | |
| 18-23 | 160 | 95.8 |
| 24-29 | 6 | 3.6 |
| 30-35 | 1 | 0.6 |
| Gender | | |
| Male | 31 | 18.6 |
| Female | 136 | 81.4 |
| Educational Status | | |
| High School | 28 | 16.8 |
| Vocational High School | 39 | 23.4 |
| Anatolian-Science High School | 100 | 59.9 |
| Income status | | |
| Bad | 21 | 12.6 |
| Medium | 130 | 77.8 |
| Good | 16 | 9.6 |
| Working status | | |
| Working | 14 | 8.4 |
| Not working | 153 | 91.6 |
| Total | 167 | 100.0 |

### Reliability of Undergraduate Nursing Clinical Evaluation Form (CEF)

The reliability coefficient obtained in the study of Porter *et al*. [8] and reliability coefficients obtained in our study are given in Table 4. When the Cronbach's α reliability coefficients were examined, the reliability of the form was found to be quite good in terms of domains and total score. Pearson's Moment Correlation Coefficient was calculated for the CEF items used in the study and the internal consistency of each item with the scale as a whole was determined (Table 5). The correlations between the items and total scale score ranged between 0.42 and 0.77, and the Cronbach's α coefficient was greater than 0.90 for each item. According to the results of the item analysis, it was found that the reliability of the form was good.

**Table 2.** **Frequency distribution of the clinical evaluation form scores**

| Domains/Items | Never n (%) | Rarely n (%) | Sometimes n (%) | Often n (%) | Always n (%) | Mean ± SD |
|---|---|---|---|---|---|---|
| **Domain: Orientation** | | | | | | **3.32 ± 0.82** |
| 1. Orientation was relevant and well organized | 10 (6) | 23 (13.8) | 66 (39.5) | 55 (32.9) | 13 (7.8) | 3.23 ± 0.99 |
| 2. I was made to feel welcome by the educator | 5 (3) | 15 (9) | 55 (32.9) | 69 (41.3) | 23 (13.8) | 3.54 ± 0.94 |
| 3.Clinical expectations were defined and discussed during orientation | 13 (7.8) | 24 (14.4) | 63 (37.7) | 50 (29.9) | 17 (10.2) | 3.2 ± 1.06 |
| **Domain: Clinical educator/Clinical teacher** | | | | | | **3.59 ± 0.76** |
| 4.The educator was available and easily contactable during placement | 2 (1.2) | 19 (11.4) | 58 (34.7) | 53 (31.7) | 35 (21) | 3.6±0.98 |
| 5.The educator was approachable and friendly | 3 (1.8) | 16 (9.6) | 46 (27.5) | 69 (41.3) | 33 (19.8) | 3.68 ± 0.96 |
| 6.Debriefing sessions were relevant and educational. | 4 (2.4) | 17 (10.2) | 65 (38.9) | 51 (30.5) | 30 (18) | 3.51 ± 0.98 |
| 7.The in-service and educational sessions were relevant | 5 (3) | 14 (8.4) | 63 (37.7) | 54 (32.3) | 31 (18.6) | 3.55 ± 0.99 |
| 8.Rosters were available to me in a reasonable timeframe | 8 (4.8) | 17 (10.2) | 47 (28.1) | 57 (34.1) | 38 (22.8) | 3.6 ± 1.09 |
| **Domain: Ward staff/preceptors and ward environment** | | | | | | **3.1 ± 0.95** |
| 9.The staff were friendly and approachable | 8 (4.8) | 33 (19.8) | 59 (35.3) | 49 (29.3) | 18 (10.8) | 3.22 ± 1.04 |
| 10.I was made to feel welcome on the ward | 11 (6.6) | 32 (19.2) | 49 (29.3) | 56 (33.5) | 19 (11.4) | 3.24 ± 1.09 |
| 11.The staff facilitated learning opportunities for me | 8 (4.8) | 27 (16.2) | 60 (35.9) | 46 (27.5) | 26 (15.6) | 3.33 ± 1.07 |
| 12.The staff involved me in clinical decision making | 37 (22.2) | 48 (28.7) | 36 (21.6) | 34 (20.4) | 12 (7.2) | 2.62 ± 1.24 |
| **Domain: Final assessment/clinical hurdles** | | | | | | **3.26 ± 0.93** |
| 13.Clinical hurdles were achieved in corporation with the clinical educator | 7 (4.2) | 26 (15.6) | 54 (32.3) | 56 (33.5) | 24 (14.4) | 3.38 ± 1.05 |
| 14.Clinical hurdles were achievable within the time frame of the clinical placement | 10 (6) | 26 (15.6) | 58 (34.7) | 55 (32.9) | 18 (10.8) | 3.27 ± 1.04 |
| 15.An interim evaluation of clinical competencies was conducted and goals set for the remainder of placement | 15 (9) | 29 (17.4) | 55 (32.9) | 53 (31.7) | 15 (9) | 3.14 ± 1.09 |
| 16. During the final evaluation I received constructive feedback | 17 (10.2) | 18 (10.8) | 58 (34.7) | 57 (34.1) | 17 (10.2) | 3.23 ± 1.1 |
| **Domain: University** | | | | | | **3.4 ± 0.82** |
| 17. The clinical placement details were made available prior to commencement of the placement | 9 (5.4) | 19 (11.4) | 68 (40.7) | 52 (31.1) | 19 (11.4) | 3.32±1 |
| 18. Clinical hurdles. assessment tasks and University expectations were outlined by unit coordinator | 5 %3) | 17 (10.2) | 68 (40.7) | 53 (31.7) | 24 (14.4) | 3.44 ± 0.96 |
| 19. A contact person was available to answer clinical questions | 8 (4.8) | 17 (10.2) | 46 (27.5) | 67 (40.1) | 29 (17.4) | 3.55 ± 1.05 |
| 20. The clinical office was approachable and friendly | 15 (9) | 19 (11.4) | 53 (31.7) | 59 (35.3) | 21 (12.6) | 3.31 ± 1.11 |
| 21. The placement was relevant to the unit content | 7 (4.2) | 21 (12.6) | 59 (35.3) | 58 (34.7) | 22 (13.2) | 3.4 ± 1.01 |

**Table 3.** **Confirmatory factor analysis fit indices**

| Fit Indices | Turkish Form | Acceptable Values |
|---|---|---|
| $\chi^2$/SD | 2.07 | ≤ 5 |
| Comparative Fit Index (CFI) | 0.911 | ≥ 0.90 |
| Standardized Root Mean Square Residuals (SRMR) | 0.059 | ≤ 0.080 |
| Root Mean Square Error of Approximation (RMSEA) | 0.080 | ≤ 0.080 |

**Table 4.** Domains of CEF and Cronbach's α Reliability Coefficients

| Factors | Item number | Original Form | Cronbach α coefficient |
|---|---|---|---|
| **Orientation** | 3 | 0.77 | 0.77 |
| **Clinical educator/clinical teacher** | 5 | 0.76 | 0.82 |
| **Ward staff/preceptors and ward environment** | 4 | 0.91 | 0.88 |
| **Final assessment/clinical hurdles** | 4 | 0.73 | 0.89 |
| **University** | 5 | 0.79 | 0.86 |
| **Total** | 21 | 0.90 | 0.94 |

**Table 5.** Results of Individual Item Analysis for CEF

| | Scale Mean if Item is Deleted | Scale Variance if Item is Deleted | Corrected Item-Total Correlation | Cronbach's Alpha if Item Deleted |
|---|---|---|---|---|
| **Item 1** | 67.1377 | 197.372 | 0.525 | 0.936 |
| **Item 2** | 66.8263 | 196.482 | 0.587 | 0.935 |
| **Item 3** | 67.1617 | 193.389 | 0.622 | 0.935 |
| **Item 4** | 66.7665 | 194.144 | 0.649 | 0.934 |
| **Item 5** | 66.6886 | 194.517 | 0.653 | 0.934 |
| **Item 6** | 66.8503 | 194.646 | 0.631 | 0.934 |
| **Item 7** | 66.8144 | 194.453 | 0.635 | 0.934 |
| **Item 8** | 66.7665 | 198.614 | 0.425 | 0.938 |
| **Item 9** | 67.1497 | 194.297 | 0.606 | 0.935 |
| **Item 10** | 67.1257 | 192.653 | 0.627 | 0.935 |
| **Item 11** | 67.0359 | 194.444 | 0.578 | 0.935 |
| **Item 12** | 67.7485 | 194.876 | 0.478 | 0.938 |
| **Item 13** | 66.9820 | 190.259 | 0.746 | 0.932 |
| **Item 14** | 67.0958 | 189.425 | 0.779 | 0.932 |
| **Item 15** | 67.2216 | 188.957 | 0.756 | 0.932 |
| **Item 16** | 67.1317 | 190.766 | 0.686 | 0.933 |
| **Item 17** | 67.0479 | 196.564 | 0.546 | 0.936 |
| **Item 18** | 66.9222 | 194.000 | 0.671 | 0.934 |
| **Item 19** | 66.8144 | 192.297 | 0.673 | 0.934 |
| **Item 20** | 67.0539 | 191.244 | 0.662 | 0.934 |
| **Item 21** | 66.9641 | 194.204 | 0.630 | 0.934 |

n = 167, No. of Items = 21, Cronbach's Alpha = 0.940

## DISCUSSION

In this study, conducted to determine the validity and reliability of the Turkish version of the CEF developed by Porter *et al*. [8], the opinions of ten experts about language and content validity were obtained The fit index of the form in terms of items and scale was found to be greater than 0.90. The data obtained from the study shows that the language and content validity of the form was ensured and that the form measures

the subject sufficiently.

### Construct Validity of Undergraduate Nursing Clinical Evaluation Form (CEF)

The construct validity of the 21-item CEF and its five domains, (orientation, clinical educator/teacher, ward staff and environment, clinical hurdles, and university) was investigated through CFA. In the CFA, a number of fit indices are used to determine the construct validity of the scale. Fit indices are used in order to evaluate the fitness between the theoretical model and the actual data. Since the fit indices have different advantages compared to each other, it is recommended that more than one fit index be used in the CFA [24]. Accordingly, it was determined that the chi-square value of the model tested with the CFA was significant ($\chi2$=370.543; $p < 0.001$). Moreover, it is stated that the possibility that the chi-square test will be significant may increase significantly with an increase in the sample size and it is recommended that the $\chi2$/SD ratio be considered [25]. In order to test which CFA model best represented the present dataset several fit indices were selected: root-mean-squared error of approximation (RMSEA) [26], comparative fit index (CFI) [27], chi-square, and change in chi-square/degrees of freedom between models [25]. RMSEA is a measure of the average of the residual variance and covariance; good models have RMSEA values that are at or less than 0.08 [8]. CFI is an index that falls between 0 and 1, with values greater than 0.90 considered to be indicators of good fitting models [28]. In the current study, the $\chi2$/SD, CFI, SRMR, and RMSEA values were found to be within acceptable limits. It can therefore be stated that the study provides construct validity.

### Reliability of Undergraduate Nursing Clinical Evaluation Form (CEF)

The Cronbach's α coefficient indicates whether the items measure the same characteristic and whether the items are associated with the measured subject. This value should be as close to 1 as possible in scales. A value between 0.60 and 0.80 indicates that the scale is very reliable; a value between 0.80 and 1.00 indicates that the scale is highly reliable [29, 30, 31, 32, 33, 34]. When the Cronbach's α reliability coefficients obtained in our study were examined, the reliability of the Turkish version of the Clinical Evaluation Form (CEF) was found to be good in terms of the domains and the total score. In the original study, the Cronbach's α values of the form in terms of domains and total score were also found to be greater than 0.70 [8]. This result shows that the Turkish version of the form is similar to the original version and has a strong internal consistency.

The correlation coefficient is an indicator of whether the items in the scale measure the desired quality in item analysis [29-32, 34, 35]. This value should be greater than 0.20 in a positive direction [30]. In our study, the correlation of items with the total scale score ranged between 0.42 and 0.77. Item-total score correlation coefficients were found to be in a positive direction and greater than 0.20. According to these results, it can be stated that all items of the scale had a high correlation with total score, that the desired quality of the scale was measured sufficiently, and that the item reliability of the scale was high. Since item-total score correlations were not given in the original study, our results could not be compared with the original form [8].

## CONCLUSION

In conclusion, clinical practice can only be successful if the instructor is able to comprehensively evaluate the process and eliminate any deficiencies. In this process, obtaining feedback from students about their clinical practice is very important. Thanks to this feedback, problems can be detected and the necessary precautions taken; thus, a more effective learning environment can be achieved. There is thus a need for a valid and reliable evaluation tool that students can use to correctly evaluate their experience of the process. This study has demonstrated that the Turkish version of the CEF is a valid and reliable measurement tool. It is suggested that nursing students use this form to evaluate clinical practice and thus eliminate a significant gap in this field.

*Authors' Contribution*

Study Conception: BA, SP, DY, NV; Study Design: BA, SP, DY, NV; Supervision: BA; Funding: BA, SP, DY, NV; Materials: BA, SP, DY, NV; Data Collection and/or Processing: BA, SP, DY, NV; Sta-

tistical Analysis and/or Data Interpretation: BA, SP, DY, NV; Literature Review: BA, SP, DY, NV; BA, SP, DY, NV: BY, MOK, EP and Critical Review: BA, SP, DY, NV.

*Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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# Presenting characteristics, comorbidities, and outcomes among 390 patients hospitalized with COVID-19 pneumonia in a tertiary hospital

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## ABSTRACT

**Objectives:** In this study, demographic characteristics, comorbidities, presenting symptoms, physical examination findings, laboratory findings, and administered drugs of the discharged or deceased patients admitted to our hospital and hospitalized with the COVID-19 diagnosis were compared to investigate the factors that affect mortality.

**Methods:** A retrospective study was performed and included COVID-19 pneumonia patients. 390 consecutive discharged or deceased patients, who were hospitalized in our hospital between March 20 and May 20, 2020, after detection of pneumonia and diagnosis of COVID-19, were included in the study.

**Results:** Of the 390 patients included in the study, 352 (90.25%) were discharged after recovery, while 38 (9.75%) were deceased. The average age of all the patients was 49.46 ± 17.86 years, the average age of the discharged patients was 47.19 ± 16.76 years, and the average age of the deceased patients was 70.42 ± 13.7 years. The average age of deceased patients was significantly higher. Of all the patients, 40.8% was PCR positive.

**Conclusions:** The present study revealed that the drugs that patients take due to their comorbidities have no effect on the prognosis of the disease and that the presence of comorbidity itself is indicative of the poor prognosis. Taking into account the PCR positivity of 57.9%, even in deceased patients, we believe PCR is inadequate in the diagnosis, and CT is much more valuable in this regard.

**Keywords:** COVID-19 disease, CT images, pneumonia, reverse transcription polymerase chain reaction

Since December 2019, the new Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) outbreak has turned from a small unknown atypical pneumonia cluster into a global pandemic. Coronavirus disease 2019 (COVID-19) now affects over 200 countries with more than 11 669 259 confirmed cases and nearly 539 906 deaths worldwide [1]. SARS-CoV-2 has similar features to Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS) coronavirus, and enters the cells through Angiotensin-Converting Enzyme 2 (ACE2) receptor, as the main entry point to infect cells [2, 3].

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Its mortality rate varies according to age and the presence of a chronic disease. While the mortality rate is 0.2% in healthy young adults, this rate is >10% in the elderly with chronic diseases [4]. Limited information has been available to describe the presenting characteristics and outcomes of COVID-19 patients requiring hospitalization in Turkey. In a retrospective cohort study from China, hospitalized patients were predominantly men with a median age of 56 years; 26% required intensive care unit (ICU) care, and there was a 28% mortality rate [5]. Italy is among the most severely affected countries, with 242.173 confirmed cases, 34.026 deaths, and an observed lethality rate of 14.1%, according to the most recent estimates of July 9th, 2020 [6]. Turkey has reported total of 209.962 confirmed cases along with 5300 deaths due to COVID-19 until July 9th, 2020 [7]. Although it is not yet possible to say anything about the differences between mortality rates, there are differences between demographic characteristics and comorbidity prevalences[8]. Research on the potentially modifiable risk factors related to the increased susceptibility to infection or worse outcomes among those infected, focuses on cardiovascular comorbidity, cerebrovascular diseases, hypertension, and diabetes [8, 9].

In this study, demographic characteristics, comorbidities, presenting symptoms, physical examination findings, laboratory findings, and administered drugs of the discharged or deceased patients admitted to our hospital and hospitalized with the COVID-19 diagnosis were compared to investigate the factors that affect mortality.

## METHODS

Following the approval of the ethics committee of our hospital for this retrospective research, 390 consecutive discharged or deceased patients, who hospitalized in our hospital between March 20 and May 20, 2020, after detection of pneumonia and diagnosis of COVID-19, were included in the study. Patients whose hospitalization continued, patients under the age of 18, patients with CT findings incompatible with COVID-19 pneumonia, and patients whose data were not available were excluded from the study.

All the patients had specific symptoms of COVID-19 infection, specific signs of viral pneumonia were present in computerized thoracic tomography (CT) in addition to laboratory findings. Infection in 159 patients was confirmed using reverse transcription polymerase chain reaction (RT-PCR). Two hundred thirty-one patients with negative RT-PCR results were diagnosed with COVID-19 by clinical, laboratory and imaging findings in accordance with Ministry of Health COVID-19 guidelines. In line with our hospital protocol, all COVID-19 patients underwent a detailed history, electrocardiography, standard biochemical and hematological tests after their admission to the emergency room. Patients included in the study were treated in accordance with the COVID-19 guidelines of the Ministry of Health. The patients were divided into two groups: those who were recovered and discharged and those who were deceased.

Clinical data of all patients, including gender, age, risk factors (coronary artery disease, chronic obstructive pulmonary disease, etc.) drugs used were collected through the hospital information management system and Social Security Institution Medulla system.

The institutional ethics board of the Gazi Yasargil Training and Research Hospital, an affiliate of the University of Health Science, reviewed and approved this retrospective study.

### Statistical Analysis

The SPSS Version 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) was used for statistical analysis. The normality of data was tested by using the Kolmogorov Smirnov test, continuous variables were compared with the Mann Whitney U test, and categorical variables were compared using the chi-square test. A $p$ - value of $< 0.05$ was considered significant.

## RESULTS

Of the 390 patients included in the study, 352 (90.25%) were discharged after recovery, while 38 (9.75%) were deceased. The average age of all the patients was 49.46 ± 17.86 years, the average age of the discharged patients was 47.19 ± 16.76 years, and the average age of the deceased patients was 70.42 ± 13.7 years. The average age of the deceased patients was significantly higher ($p < 0.001$). Of all the patients,

**Table 1. Clinical findings of patients with COVID-19 pneumonia**

| | All patients (n = 390) | Discharged (n = 352) | Exitus (n = 38) | *p* value |
|---|---|---|---|---|
| Age (years) | 49.46 ± 17.86 | 47.19 ± 16.76 | 70.42 ± 13.7 | < 0.001 |
| Sex | | | | |
| Female | 188 (48.2) | 171 (48.6) | 17 (44.7) | 0.652 |
| Male | 202 (51.8) | 181 (51.4) | 21 (55.3) | |
| PCR result, n (%) | | | | |
| Negative | 231 (59.2) | 215 (61.1) | 16 (42.1) | 0.024 |
| Positive | 159 (40.8) | 137 (38.9) | 22 (57.9) | |
| First symptom onset to admission, days | 5.32 ± 2.81 | 5.33 ± 2.89 | 5.18 ± 1.93 | 0.733 |
| Symptoms, n (%) | | | | |
| Fever | 149 (38.2) | 133 (37.8) | 16 (42.1) | 0.602 |
| Cough | 203 (52.1) | 183 (52.0) | 20 (52.6) | 0.94 |
| Dispne | 88 (22.6) | 70 0 (19.9) | 18 (47.4) | **< 0.001** |
| Sputum | 9 (2.3) | 8 (2.3) | 1 (2.6) | 0.88 |
| Sore throat | 40 (10.3) | 34 (9.7) | 6 (15.8) | 0.23 |
| Myalgia | 47 (12.1) | 41 (11.6) | 6 (15.8) | 0.45 |
| Chest distress | 13 (3.3) | 11 (3.1) | 2 (5.3) | 0.48 |
| Smell and taste disorders | 8 (2.1) | 8 (2.3) | 0 | 0.34 |
| Diarrhea | 12 (3.1) | 10 (2.8) | 2 (5.3) | 0.41 |
| Headache | 20 (5.1) | 19 (5.4) | 1 (2.6) | 0.46 |
| Nausea, vomiting | 19 (4.9) | 19 (5.4) | 0 | 0.14 |
| Fatigue | 117 (30.0) | 107 (30.4) | 10 (26.3) | 0.6 |
| Systolic blood pressure | 116.53 ± 13.26 | 116.12 ± 12.8 | 120.32 ± 16.69 | 0.560 |
| Diastolic blood pressure | 72.1 ± 8.43 | 72.08 ± 8.26 | 72.24 ± 10 | 0.41 |
| Temperature (°C) | 37.1 ± 0.61 | 37.11 ± 0.61 | 37.09 ± 0.68 | 0.58 |
| Pulse rate | 84.22 ± 12.64 | 84.25 ± 12.49 | 83.97 ± 14.15 | 0.47 |
| Oxygen saturation | 96,17 ± 4.15 | 96.84 ± 3.49 | 90.03 ± 4.78 | **< 0.001** |
| Underlying comorbidities, n (%) | 153 (39.2) | 122 (34 7) | 31 (81.6) | **< 0.001** |
| Hypertension | 82 (21.0) | 59 (16.8) | 23 (60.5) | **< 0.001** |
| Diabetes | 59 (15.2) | 47 (13.4) | 12 (31.6) | **0.003** |
| Chronic obstructive pulmonary disease | 42 (10.8) | 34 (9.7) | 8 (21.1) | **0.032** |
| Chronic Heart Disease | 39 (10.0) | 33 (9.4) | 6 (15.8) | 0.211 |
| Malignancy | 6 (1.5) | 5 (1.4) | 1 (2.6) | 0.56 |
| Chronic Kidney Disease | 12 (3.1) | 11(3.1) | 1 (2.6) | 0.86 |
| Cerebrovascular diseases | 9 (2.3) | 6 (1.7) | 3 (7.9) | **0.016** |
| Dementia | 4 (10) | 2 (0.6) | 2 (5.3) | **0.006** |
| Medications Used by COVID-19 Patients Before Admission, n (%) | | | | |
| Antithrombotic | 61 (15.6) | 43 (12.2) | 18 (47.4) | **< 0.001** |
| Diuretic | 31 (7.9) | 22 (6.3) | 9 (23.7) | **< 0.001** |
| Beta blocker | 44 (11.3) | 35 (9.9) | 9 (23.7) | **0.011** |
| Calcium channel blockers | 48 (12.3) | 34 (9.7) | 14 (36.8) | **< 0.001** |
| ACE inhibitor | 25 (6.4) | 21 (6.0) | 4 (10.5) | 0.27 |
| Angiotensin receptor blocker | 34 (8.7) | 22 (6.3) | 12 (31.6) | **< 0.001** |
| Oral antidiabetic | 43 (11.1) | 35 (9.9) | 8 (21.6) | **0.031** |
| Insulin | 20 (5.1) | 13 (3.7) | 7 (18.4) | **< 0.001** |
| Inhaled drugs | 40 (10.3) | 32 (9.1) | 8 (21.1) | **0.021** |
| Stay at hospital (days) | 10.18 ± 8.02 | 9.65 ± 5.87 | 15.08 ± 17.94 | 0.224 |

Data are shown as mean ± standard deviation or n (%)

**Table 2. Laboratory findings of patients with COVID-19 pneumonia**

| | All patients (n = 390) | Discharged (n = 352) | Exitus (n = 38) | *p* value |
|---|---|---|---|---|
| WBC ($10^9$ /L) | 8.1 ± 5.59 | 7.63±4.22 | 12.5 ± 11.73 | **0.001** |
| Neutrophil ($10^9$ /L) | 5.77 ± 4.46 | 5.54 ± 4 | 7.86 ± 7.21 | 0.46 |
| Lymphocyte ($10^9$ /L) | 1.78 ± 2.47 | 1.67 ± 0.76 | 2.8 ± 7.57 | **< 0.001** |
| Platelets ($10^9$ /L) | 232.92 ± 83.52 | 232.84±79.92 | 233.66 ± 112.9 | 0.638 |
| Hb (g/dL) | 13.49 ± 2.05 | 13.59±1.95 | 12.61 ± 2.69 | **0.011** |
| Htc (%) | 41.74 ± 5.67 | 42.1±5.04 | 38.43 ± 9.23 | **0.003** |
| Albumin (g/L) | 42.43 ± 5.62 | 43.36 ± 4.48 | 33.79 ± 7.58 | **< 0.001** |
| ALT (U/L) | 28.88 ± 32.05 | 28.32 ± 26.42 | 34.08 ± 64.39 | 0.69 |
| AST (U/L) | 31.28 ± 34.61 | 29.39 ± 26.34 | 48.76 ± 75.25 | **0.002** |
| CRP (mg/L) | 51.33 ± 68.44 | 40.95 ± 58.55 | 147.51 ± 78.7 | **<0.001** |
| Ca (mg/dL) | 8.58 ± 0.5 | 8.63 ± 0.46 | 8.1 ± 0.56 | **< 0.001** |
| Cl (mmol/ L) | 103.48 ± 4.2 | 103.34 ± 3.29 | 104.84 ± 8.95 | 0.905 |
| Creatinin (mg/dL) | 0.96 ± 0.78 | 0.91 ± 0,76 | 1.4 ± 0.84 | **< 0.001** |
| LDH (U/L) | 280.75 ±1 29.05 | 267.69 ± 116.95 | 401.68 ± 169.41 | **< 0.001** |
| K (mmol / L) | 4.11 ± 0.51 | 4.09 ± 0.49 | 4.28 ± 0.66 | 0.167 |
| Na (mEq/L) | 137.16 ± 3.53 | 137.16 ± 2.74 | 137.08 ± 7.71 | 0.02 |
| Urea (mg/dL) | 33.33 ± 28.03 | 29.25 ± 20.02 | 71.11 ± 53.27 | **< 0.001** |
| D-dimer (ng/mL) | 395,05 ± 553,88 | 342,24 ± 480,2 | 884,21 ± 875,02 | **< 0.001** |
| Troponin (ng/mL) | 0.14 ± 0.39 | 0.13 ± 0.35 | 0.25 ± 0.66 | **< 0.001** |

Data are shown as mean ± standard deviation or n (%)

40.8% was PCR positive. PCR positivity was significantly higher by 57.9% in deceased patients ($p$ = 0.024). There were no gender differences between the two groups and in all patients (Table 1).

The duration between symptom onset and hospitalization was 5.32 ± 2.81 days in all patients included in the study. The most common symptoms were cough by 52.1%, fever by 38.2%, and fatigue by 30%, respectively. In the comparison of the symptoms of the patient groups, there was no significant difference between symptoms other than dyspnea, and the incidence of dyspnea was found to be higher in deceased patients (47.4%) than in the discharged patients (19.9%) ($p < 0.001$).

According to the results of the physical examination between the groups, the mean saturation in deceased patients was 90%, and 96% in the discharged patients. The mean saturation was significantly lower in the deceased group ($p < 0.001$).

The presence of comorbidity was significantly

**Tablo 3. CT features of patients with COVID-19 pneumonia**

| | Total | Discharged | Exitus | *p* value |
|---|---|---|---|---|
| Ventral and dorsal | 62 (15.9) | 41 (11.6) | 21 (55.3) | **< 0.001** |
| Bilateral | 291 (74.6) | 254 (72.2) | 37 (97.4) | **0.001** |
| Perihilar | 89 (22.8) | 72 (20.5) | 17 (44.7) | **0.001** |
| Peripheral | 359 (92.1) | 325 (92.3) | 34 (89.5) | 0.536 |

Data are shown as n (%)

higher in the deceased group ($p < 0.001$).). The most common additional disease in the deceased group was hypertension by 60%. HT, DM, cerebrovascular disease and dementia were significantly higher in the deceased group ($p < 0.001$, $p = 0.003$, $p = 0.016$ and $p = 0.006$, respectively) (Table 1).

Considering the drug use in the deceased group, antithrombotic, diuretic, beta blocker, ARB, calcium channel blocker, oral antidiabetic and insulin use was significantly higher ($p < 0.001$, $p < 0.001$, $p = 0.011$, $p < 0.001$, $p < 0.001$, $p = 0.031$ and $p < 0.001$, respectively), whereas there was no statistical difference in the use of ACE inhibitors compared to the discharged patients ($p = 0.27$).

In the examination of the laboratory findings of the patient groups, hemogram parameters leukocyte and lymphocyte counts were significantly higher in the deceased patients ($p = 0.001$ and $p < 0.001$, respectively), while hemoglobin and hematocrit levels were significantly lower ($p = 0.011$, $p = 0.003$, respectively) (Table 2).

Of the biochemical parameters, albumin was significantly lower, while CRP, LDH, urea, creatine, D-dimer and troponin were significantly higher ($p < 0.001$).

In the evaluation of lung involvement in thoracic CT, perihilar involvement, ventral and dorsal involvement, and bilateral lung involvement were significantly higher in the deceased patients ($p < 0.001$) (Tablo 3) (Fig. 1).

## DISCUSSION

In the study, advanced age and comorbid factors such as hypertension and diabetes were found to be significantly higher in deceased patients in line with the literature. In deceased patients, the most common comorbidity was hypertension by 60%, in line with the literature [8, 10]. Although preliminary studies reported higher COVID-19 incidence in the male gender, subsequent studies found no difference between

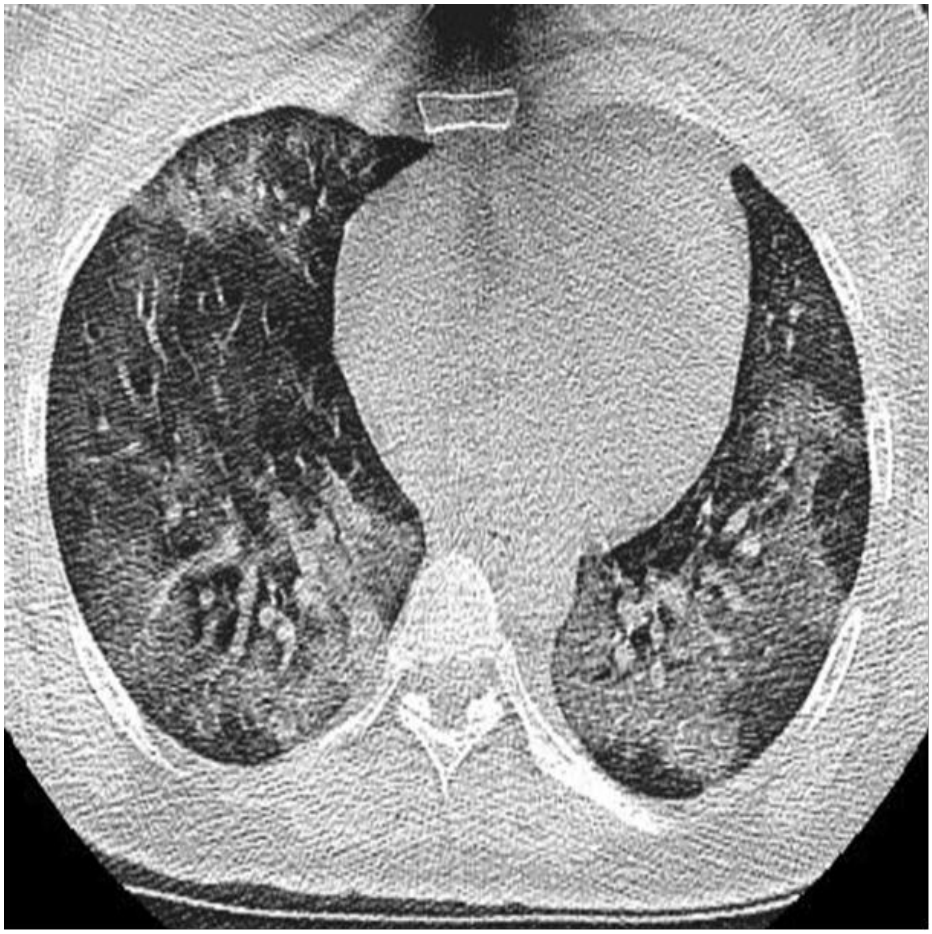

**Fig.1. CT scan of 53-year old female with COVİD-19. Bilateral ventral and dorsal located ground glass opacities.**

the genders as in the present study [11, 12]. We believe, the higher infection incidence in the male gender in the preliminary research was due to the fact that most of affected patients associated with the seafood wholesale market were male workers.

The most common presenting symptoms of the patients were cough by 52.1%, fever by 38.2%, and fatigue by 30%, respectively, in line with the literature [8, 13]. As expected, dyspnea incidence was higher in the deceased group, and thus saturations were lower. Some studies have reported that ACE/ARB use increases mortality [3, 14-16]. However, many studies and meta-analysis studies have shown no such risk [17–19], and major cardiology scientific associations, including the ACC, HFSA, AHA, and ESC Hypertension Council, have rejected these correlation hypotheses [20]. The significantly higher use of antithrombotics, diuretics, beta blockers, ARBs, calcium channel blockers, oral antidiabetics and insulin in the deceased group in the study is believed to be due to the presence of hypertension and diabetes, not the drugs used. Although the use of all antihypertensives was significantly higher in the deceased group compared to the discharged group, it is important to note that the use of ACE inhibitors did not differ between the groups, indicating that the use of ACE inhibitors does not increase the risk of mortality.

In the laboratory findings, the infection indicators CRP, leukocyte and albumin (as negative acute phase reactants) were significantly different between the two groups as expected. (Table 2). In the deceased group, CRP, LDH, urea, creatine, D-dimer, troponin, leukocyte and lymphocyte levels were significantly higher, while albumin, hemoglobin, and hematocrit levels were significantly lower. Many studies have shown similar results to our findings, but despite the fact that lymphopenia was observed in COVID-19 patients with particularly poor prognosis and in many patients in our study, the mean lymphocyte levels in both groups were within the normal limits, but the lymphocyte count in deceased patients was found to be significantly higher compared to discharged patients [10–12].

Laboratory values suggest that COVID-19 infection may be associated with cellular immunodeficiency, coagulation activation, myocardial damage, hepatic damage, and kidney damage. We believe that the cause of mortality in COVID-19 pneumonia is hypoxia and shock caused by the direct effect of the virus, and the cytokine storm that develops due to inflammatory response.

In the evaluation of lung involvement in thoracic CT, perihilar involvement, ventral and dorsal involvement, and bilateral lung involvement were significantly higher in the deceased patients. In the literature review, it was found that there are findings indicating that bilateral lung involvement increases mortality, similar to the results of this study [21]. However, there was no study of perihilar involvement in particular.

## CONCLUSION

The present study suggests that advanced age, presence of comorbidity, the levels of laboratory parameters such as CRP, creatine, D-dimer, troponin, hemoglobin and albumin, and bilateral and perihilar involvement in CT can be considered as a sign of poor prognosis in COVID-19 patients. The present study revealed that the presence of comorbidity itself is indicative of the poor prognosis. More comprehensive and detailed studies are needed to determine the death effect of drug use. Taking into account the PCR positivity of 57.9%, even in deceased patients, we believe PCR is inadequate in the diagnosis, and CT is much more valuable in this regard.

*Authors' Contribution*

Study Conception: EA, SA, MÖ, SA, AA; Study Design: EA, SA, MÖ, SA, AA; Supervision: EA, SA, MÖ, SA, AA; Funding: EA, SA, MÖ, SA, AA; Materials: EA, SA, MÖ, SA, AA; Data Collection and/or Processing: EA, SA, MÖ, SA, AA; Statistical Analysis and/or Data Interpretation: EA, SA, MÖ, SA, AA; Literature Review: EA, SA, MÖ, SA, AA; Manuscript Preparation: EA, SA, MÖ, SA, AA and Critical Review: EA, SA, MÖ, SA, AA.

*Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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# Prediction value of creatine kinase level in conservative treated unruptured tubal ectopic pregnancies

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## ABSTRACT

**Objectives:** An ectopic pregnancy (EP) occurs when a fertilized ovum implants outside the endometrial cavity. We investigated the creatine kinase (CK) enzyme in conservatively treated EP to determine the resolution time and predict cases that may progress to surgical intervention.

**Methods:** We include 43 patients with stable vital signs at recruitment. All participants were examined by using transvaginal ultrasound (TVUS). Beta human chorionic gonadotropin (β-hCG) and creatine kinase (CK) levels were also measured. In cases diagnosed with EP, intramuscular methotrexate (MTX) at a dose of 50 mg / m2 was administered and monitored with β-hCG titers. Follow-up continued until β-hCG titer became negative, or surgery became mandatory due to acute abdominal pain.

**Results:** The mean β-hCG Level in the presence of an adnexal mass was statistically significantly higher than the mean level in patients in whom TVUS failed to define a mass. The mean β-hCG level in the surgical exploration group of patients was significantly higher than in those who did not require surgery. At a cut-off of 6486 mIU/mL, β-hCG could predict the emergence of acute abdomen with a sensitivity of 75% and a specificity of 94.3%. We examined CK level to contribute the test's specificity, but we found no difference among cases with and without surgical exploration.

**Conclusions:** In patients treated conservatively for EP, CK levels at the outset neither predict an acute abdomen to emerge nor shed light on the resolution period in patients who respond to medical therapy.

**Keywords:** Ectopic pregnancy, creatine kinase enzyme, β-hCG level, methotrexate

Ectopic pregnancy (EP) is a condition when fertilized ovum implants anywhere other than the endometrial cavity [1, 2]. EP is a life-threatening condition if it is not detected, monitored, and treated in time. Many risk factors have been identified for EP [3]. We might divide them into three main groups: high, moderate, and low-risk factors. High risk is: if previous pregnancy of the patient was an EP; previous tubal surgery or tubal sterilization; tubal pathology defined by hysterosalpingography or laparoscopy; use of the intrauterine device (IUD); surgical sterilization; intrauterine diethylstilbestrol (DES) exposure. The moderate-risk group is a history of genital infections (gonorrhea, chlamydia), smoking, and patient infertility. The low-risk group includes a history of previous pelvic or abdominal surgery, vaginal douche, and early sexual intercourse in patients.

As we know, some pathophysiological changes occur in ectopic pregnancy. In the literature, 95% of EPs are tubal pregnancies [4]. The authors reported

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that implantation takes place in the lumen, and then infiltration continues extraluminal by penetrating the lamina propria and muscularis layer [5]. We already know three scenarios for tubal pregnancies: involution, tubal abortion, or rupture of EP. The rupture of the fallopian tubes occurs between 6 and 12 weeks, depending on the location and early diagnosis of the EP [6]. Ampullar EP, most common type of tubal EP. In that localization, tubal rupture most frequently occurs on the 12th of the gestational week. Isthmus is the second most common place for implantation of EP [7]. In this part of the tube, the lumen is narrow, the rupture of the tube occurs in an earlier pregnancy period.

Creatine kinase (CK) is a protein with a molecular weight of 86,000 kDa. There are three types (isoenzymes) of CK: CK-I or BB is primarily found in the brain and smooth muscle, CK-II or MB primarily in the heart, CK-III or MM primarily in skeletal muscle [8-10].

CK activity is associated with gender, age, race, and muscle mass and shows physiological variations. The reference range for women is 10-79 U/L, and men are 17-148 U/L. The height of CK occurs primarily as a result of brain, heart, or muscle damage.

CK is not a frequently used test in gynecology and obstetrics practice. Maternal serum CK level has been investigated as a marker in the diagnosis of EP. It was significantly higher in patients with tubal pregnancy than patients with missed abortion or normal intrauterine pregnancy [11]. Develioglu *et al*. [12] found out to CK levels were higher in isthmic than ampullary and higher in ruptured than in unruptured cases of EP. CK levels were higher in the isthmic localization of EP because damage to muscle infiltration in this part of the tuba occurs more rapidly in less time. Currently, the most valuable tests for the diagnosis of EP are the measurement of human beta-chorionic gonadotropin (β-hCG) in serum and transvaginal ultrasound (TVUS) screening [13].

The use of these tests separately and in combination can be diagnostic but does not always determine treatment modalities. There are previously published studies to utilize biomarkers to manage and treat the patient promptly [14, 15]. In this study, we planned to examine the CK enzyme in conservatively treated ectopic pregnancies to determine the resolution period of ectopic pregnancy and predict cases that may progress to tubal rupture.

## METHODS

Forty-three patients treated conservatively for EP at the Department of Obstetrics and Gynecology of Uludag University Medical School during the period extending from March 2004 to November 2007 were included in this study. All included cases had stable vital signs at admission evaluated by TVUS, β-hCG, and CK measurements. Exclusion criteria for this study were: patients with acute abdomen, factors that increase CK and CK-MB levels (trauma, muscle damage, intramuscular injection, diagnosed cardiac disease), and contraindication to the use of methotrexate (liver diseases, psoriasis, rheumatoid arthritis, aplastic anemia). Patients diagnosed with EP were given intramuscular MTX at a dose of 50 mg/m$^2$ and were followed up with β-hCG titers. β-hCG values were measured on the 4$^{th}$ and 7$^{th}$ days of MTX administration. Patients with the β-hCG decline of 15% or more were followed weekly until they became negative. At the same dose, the second MTX administration was given to the patient whose β-hCG titers decreased by less than 15% on the 4th and 7th days of the first MTX dose. The patients were divided into two groups according to their response to MTX treatment: medical treatment responders and group requiring surgical exploration due to acute abdomen after MTX treatment. Gestational age at the time of diagnosis, β-hCG and CK levels, and TVUS findings were determined in both groups. We also compared the mean size of the extra-ovarian mass, presence of gestational sac, mean size of gestational sac, presence and size of fetal nodes, and fetal cardiac activity in both groups. We also evaluated the factors that can affect the resolution time in MTX responded group: age of the patients, obstetric history, ectopic pregnancy history, gestation period, MTX dose, and BMI. Uludag University Faculty of Medicine Ethics Committee approved this study.

### Statistical Analysis

Continuous variables were given with their mean and standard deviations. Mann-Whitney U-test was used for intergroup comparisons, and the Spearman correlation coefficient was used to define the relationship between variables. Linear regression analysis was

used to evaluate the independent variables that were shown to be separately correlated with the dependent variable. Receiver operating characteristics (ROC) analysis was used to determine the sensitivity and specificity of the diagnostic tests. A $p < 0.05$ was considered statistically significant. SPSS 13.0 (Chicago, IL, USA) program was used for statistical evaluations.

## RESULTS

The mean gestational age of the 43 patients included in the study were 48.9 ± 13.6 days, mean age of patients 29.7 ± 5.5 years (29; 22-44), mean body weight 65.5 ± 10.3 kg; mean BMI 24.6 ± 3.3 kg/m$^2$; mean body area 1.71 ± 0.1; mean β-hCG level was 3584 ± 5165 mIU/mL; mean MTX dose was 84.7 ± 7.0 mg.

Seven patient had previous EP history. TVUS revealed an extra-ovarian adnexal mass in 31 (72.1%) patients, the mean size of the mass was measured as 21.8 ± 6.5 (20; 11-35) mm. Gestational sac within the mass in 18 (41.9%), a fetal node in 3 (7.0%), and fetal cardiac activity in 2 patients (4.7%) were found out. The β-hCG levels detected on the day of diagnosis did not show a statistically significant difference with the age of patients (r = 0.120; $p = 0.44$). Comparison of β-hCG level according to obstetric and ultrasonographic variables are presented in Table 1.

There was no relationship between β-hCG levels

**Table 1. Comparison of β-hCG levels according to obstetric and ultrasonographic variables**

| n = 43 | β-hCG level | *p* value |
|---|---|---|
| **Primigravid** | | |
| Yes (n = 16) | 3474 ± 6200 | 0.19 |
| No (n = 27) | 3650 ± 4573 | |
| **Nulliparity** | | |
| Yes (n = 29) | 3631 ± 5306 | 0.82 |
| No (n = 14) | 3488 ± 5054 | |
| **Abortion History** | | |
| Yes (n = 12) | 2448 ± 1920 | 0.34 |
| No (n = 31) | 4024 ± 5940 | |
| **Elective Curettage History** | | |
| Yes (n = 6) | 5730 ± 6992 | 0.42 |
| No (n = 37) | 3236 ± 4842 | |
| **Ectopic Pregnancy History** | | |
| Yes (n = 7) | 5070 ± 5034 | 0.12 |
| No (n = 36) | 3296 ± 5210 | |
| **Extra-overian Mass** | | |
| Yes (n = 31) | 4634 ± 5725 | **0.003** |
| No (n = 12) | 873 ± 1163 | |
| **Gestation Sac** | | |
| Yes (n = 18) | 5577 ± 6086 | 0.11 |
| No (n = 13) | 3329 ± 5128 | |
| **Fetal Node** | | |
| Yes (n = 3) | 12908 ± 5777 | **0.027** |
| No (n = 15) | 4110 ± 5137 | |

Data were presented as mean ± standart deviation.

**Table 2. Comparison of Creatine kinase levels according to obstetric and ultrasonographic variables**

| n = 43 | Creatine Kinase | *p* value |
|---|---|---|
| **Primigravid** | | |
| Yes (n = 16) | 69.8 ± 41.0 | 0.29 |
| No (n = 27) | 78.4 ± 45.8 | |
| **Nulliparity** | | |
| Yes (n = 29) | 67.2 ± 33.1 | 0.14 |
| No (n = 14) | 91.8 ± 58.4 | |
| **Abortion History** | | |
| Yes (n = 12) | 82.2 ± 54.3 | 0.55 |
| No (n = 31) | 72.5 ± 39.7 | |
| **Elective Curettage History** | | |
| Yes (n = 6) | 91.2± 56.5 | 0.57 |
| No (n = 37) | 72.6 ± 41.8 | |
| **Ectopic Pregnancy History** | | |
| Yes (n = 7) | 82.9 ± 24.8 | 0.11 |
| No (n = 36) | 73.7 ± 46.7 | |
| **Extra-ovarian Mass** | | |
| Yes (n = 31) | 81.7 ± 48.9 | 0.096 |
| No (n = 12) | 58.3 ± 19.2 | |
| **Gestation Sac** | | |
| Yes (n = 18) | 76.7 ± 47.0 | 0.31 |
| No (n = 13) | 88.8 ± 52.5 | |
| **Fetal Node** | | |
| Yes (n = 3) | 94.3 ± 83.5 | 0.95 |
| No (n = 15) | 73.1 ± 40.0 | |

Data were presented as mean± standart deviation.

and obstetric variables (Table 1). However, the mean β-hCG level of 31 patients with an extra-ovarian mass statistically significantly higher than the mean level in patients in whom TVUS failed to define a mass (4634 ± 5725 vs. 873 ± 1163 mIU/mL; $p = 0.003$). In addition, in three cases with fetal nodes, β-hCG levels are significantly higher compared to cases where gestational sacs are seen as anembryonic.

Comparison of Creatine Kinase level according to obstetric and ultrasonographic variables are presented in Table 2.

There were no relationship between CK levels and obstetric variables ($p > 0.05$). Although the mean CK level of 31 patients with an extra-ovarian mass detected TVUS seemed to be higher than those without a mass. Still, this difference was of no statistical significance ($p = 0.096$). The size of the extra-ovarian masses also did not correlate with CK levels. Additionally, CK levels detected on the day of diagnosis of EP did not show a statistically significant difference with the age of patients ($r = 0.099$; $p = 0.53$).

Surgical exploration was indicated for acute abdominal pain in eight (18.6%) patients during the follow-up after MTX administration. Characteristics of cases requiring surgical exploration are presented in Table 3.

The variables between the surgical intervention group and the medically treated group were investi-

**Table 3. Characteristics of cases requiring surgical exploration**

| Case | Gestation period (Day) | β-hCG (mIU/mL) | CK (IU/L) | US findings* | Follow-up time | Ectopic localization | Operation findings |
|---|---|---|---|---|---|---|---|
| 1 | 42 | 7133 | 54 | EM/GS | 2 | Isthmic | Rupture |
| 2 | 40 | 730 | 77 | EM/GS | 2 | Ampulla | Abortus |
| 3 | 45 | 18840 | 93 | EM | 4 | Isthmic | Rupture |
| 4 | 48 | 610 | 71 | EM/GS | 2 | Ampulla | Rupture |
| 5 | 34 | 7073 | 125 | EM | 2 | Ampulla | Abortus |
| 6 | 46 | 19101 | 36 | EM/GS/FN/FCA | 18 | Ampulla | Rupture |
| 7 | 54 | 7665 | 190 | EM/GS/FN | 5 | Ampulla | Rupture |
| 8 | 57 | 18696 | 53 | EM/GS | 24 | Ampulla | Abortus |

EM = Extra-ovarian mass, GS = Gestation sac, FN = Fetal node, FCA = Fetal cardiac activity

**Table 4. Comparison of Weight, BMI, and MTX dose in cases with and without surgical exploration.**

| | Surgical Exploration | | *p* value |
|---|---|---|---|
| | Yes (n = 8) | No (n = 35) | |
| **Weight (kg)** | 66.9 ± 8.8 | 65.2 ± 10.7 | 0.55 |
| **BMI (kg/m$^2$)** | 24.6 + 3.4 | 24.6 ± 3.3 | 0.80 |
| **MTX dose (mg)** | 81.6 ± 13.7 | 83.4 ± 9.3 | 0.77 |

Data were presented as mean ± standart deviation. BMI = Body mass index, MTX = Methotrexate döşe

**Table 5. Comparison of gestational age and β-hCG and CK levels in cases with and without surgical exploration**

| | Surgical Exploration | | *p* value |
|---|---|---|---|
| | Yes (n = 8) | No (n = 35) | |
| **Gestation age (Day)** | 45.8 ± 7.4 | 49.6 ± 14.6 | 0.84 |
| **β-hCG (mIU/mL)** | 9981 ± 7865 | 2122 ± 2898 | **0.003** |
| **CK (IU/L)** | 87.4 ± 49.7 | 72.4 ± 42.6 | 0.29 |

Data were presented as mean ± standart deviation.

gated. There was no difference between these two groups in terms of weight, BMI and MTX dose ($p > 0.05$). (Table 4)

Comparisons of the gestational age, β-hCG and CK levels between the patients with and without surgical exploration are presented in Table 5 There was no difference between the groups in terms of gestational age and CK levels on the day of the diagnosis of EP ($p > 0.05$). But the mean β-hCG level in the surgically explorated group was significantly higher (9981 ± 7865 vs. 2122 ± 2898 mIU/mL; $p = 0.003$).

According to the ROC analysis the cut-off value of β-hCG level in of ectopic pregnancy was 6486 (AUC = 0.829; SE = 0.093, Sensitivity= 75% and Specificity 94.30%) with the 90.70% accuracy level (Fig. 1).

Eight of 31 patients (25.8%) who had extra-ovarian mass at the time of hospitalization required surgery. But an acute abdomen did not develop in any of the patients whose extra-ovarian mass could not be

identified by TVUS. For the prediction of acute abdomen, identification of an extra-ovarian adnexal mass had a sensitivity of 100%, with the specificity of 34.3%. In the subgroup that underwent surgery among patients with extra-ovarian mass, the mean size of mass, defined as (25.6 ± 7.9 [22; 18-35]) mm, were larger than in patients without an surgery intervention (20, 5 ± 5.5 [20]); 11-31] mm) with ($p$ = 0.10).

According to the ROC analysis, the theoretical accuracy rate of extra-ovarian mass dimensions in predicting the development of acute abdomen due to EP was 69.8% (AUC = 0.698; SE = 0.110, Sensitivity = 100% and Specificity = 30.40%) (Fig. 2).

In 35 patients who did not undergo surgery, EP recovered in an average of 24.8 ± 12.4 days following MTX administration. We found no correlation between MTX doses and β-hCG (r = -0.063; $p$ = 0.69), CC (r = 0.254; $p$ = 0.10) levels. The resolution period was longer in patients with higher β-hCG levels at the outset (r=0.556; $p$ = 0.001). The presence of an adnexal mass was also an independent determinant of the regression in β-hCG levels that reflected the resolution of EP ($p$ = 0.081). CK levels at admission were not predictive of this resolution time.

Comparison of resolution period according to obstetric and ultrasonographic variables in patients with MTX response is presented in Table 6.

There was no relationship between the resolution period and ultrasonographic variables obstetric variables except primigravid. We found that the resolution period was shorter in primigravida patients (20.6 ± 12.1, 27.6 ± 12.7; $p$ = 0.048).

## DISCUSSION

EP incidence dramatically increased in the last two decades. Every woman in reproductive age admitted to the emergency department with abdominal pain should be investigated for EP. Early diagnosis reduces complications and mortality from EP and allows patients to be treated conservatively [16].

Some of the EP resolves spontaneously without medical treatment or surgical intervention [7]. Current research shows no available method that differentiates which cases can progress to rupture of the fallopian tubes and have to be treated surgically as a first-line treatment. In our study, we aimed to investigate creatine kinase (CK) levels for this purpose.

Lavie *et al*. [11] conducted CK research as a marker for EP diagnosis. In their study, CK levels were significantly higher in tubal EP than in missed abortion and intrauterine pregnancies. Elevation of CK level in maternal serum has been explained by damage caused by the invasion of trophoblasts in the muscular layer of the Fallopian tube.

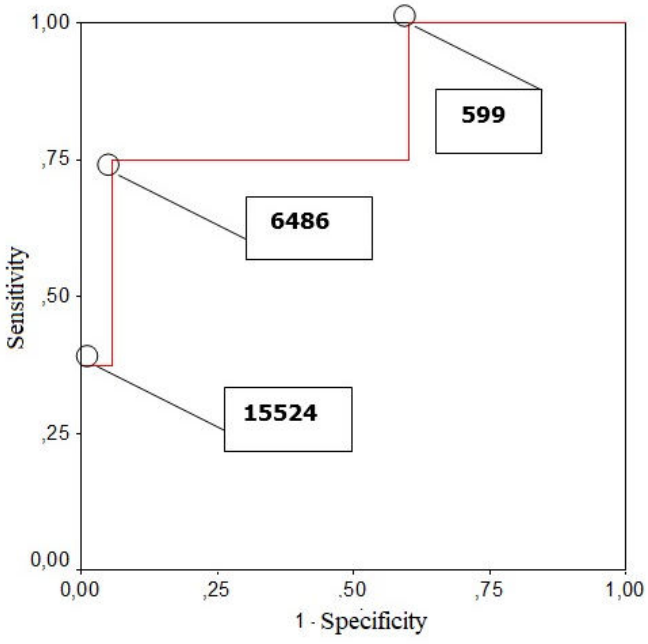


**Fig. 1. The value of β-hCG in predicting acute abdomen.**

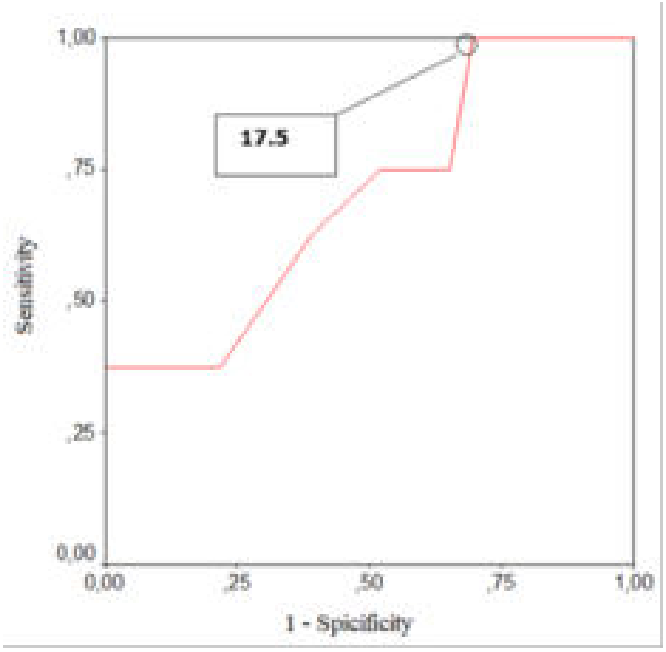


**Fig. 2. The value of extra-ovarian mass size in predicting the acute abdomen.**

**Table 6. Resolution period in responders to methotrexate therapy**

| n = 35 | Resolution Period (Day) | *p* value |
|---|---|---|
| **Primigravid** | | |
| Yes (n = 14) | 20.6 ± 12.1 | **0.048** |
| No (n = 21) | 27.6 ± 12.7 | |
| **Nulliparity** | | |
| Yes (n = 25) | 25.0 ± 14.0 | 0.68 |
| No (n = 10) | 24.1 ± 7.7 | |
| **Abortion history** | | |
| Yes (n = 11) | 28.7 ± 14.7 | 0.22 |
| No (n = 24) | 23.0 ± 11.1 | |
| **Elective curettage history** | | |
| Yes (n = 4) | 22.0 ± 3.6 | 0.99 |
| No (n = 31) | 25.1 ± 13.1 | |
| **Ectopic pregnancy history** | | |
| Yes (n=6) | 30.3 ± 9.7 | 0.084 |
| No (n=29) | 23.6 ± 12.8 | |
| **Extra-ovarian mass** | | |
| Yes (n = 23) | 27.0 ± 13.0 | 0.099 |
| No (n = 12) | 20.4 ± 10.5 | |
| **Gestation sac** | | |
| Yes (n = 12) | 28.4 ± 12.0 | 0.12 |
| No (n = 23) | 22.9 ± 12.5 | |

Data were presented as mean± standart deviation.

However, most other studies in the literature disagree with Lavie *et al*. [11]'s study. Vandermolen *et al*. [17] found that the Level of CK at EP was within the normal range, and there is no diagnostic value of creatine in EP. Sarı *et al*. [18] found out in their study what the CK levels of the induced, spontaneous, or missed miscarriages and EP were not significantly different. Horne *et al*. [19] noted that biomarkers had been studied extensively about EP, but the results have been so conflicting that none have been put into clinical use. And they have also pointed out the limitation of the clinical utility of markers because of the variable results of studies.

Develioğlu *et al*. [12], in their study, examined 32 tubal ectopic pregnancies which are undergoing salpingectomy. In ruptured isthmic ectopic pregnancies, β-HCG levels were lower, but CK levels were higher than in other EP localizations. An elevated CK level in isthmic localization was explained with rapid invasion progression in a shorter time [12].

Seven of our cases (16.3%) had a history of the previous EP. This finding confirmed that it increases the risk of recurrence of ectopic in patients with a previous EP [20].

Our data shows that the duration of pregnancy and the results of TVUS are not related. On the other hand, TVUS results were more closely correlated with β-hCG levels. These findings suggest a similar inference to the study by Sivalingam et al. [14]. They highlight the importance of using a combination of TVUS and beta-hCG in the diagnosis of EP [14].

Tawfiq *et al*. [21]'s study pointed out that MTX should not be used to treat EP when initial beta-hCG is > 4000 IU/L.

In our study, we found that the most effective producers for acute abdomen were β-hCG values of ≥

6486 mIU/ml and above, and an extraovarian mass of ≥ 17.5 mm. Combining these tests has a very high sensitivity, but low specificity creates diagnostic inadequacy in predicting acute abdominal development due to EP. To increase the specificity of diagnostic tests, we aimed to benefit from CK levels in our study. Previously, Develioğlu *et al*. [12] examined CK in this prospect and found that the highest CK values were founded in ruptured isthmic pregnancy. In our study, for patients with adnexal mass greater than 17.5 mm defined by TVUS, the mean CK level (86.6 ± 57.3) of the patients without acute abdomen was not different from the patients with acute abdomen with the mean CK level (87.4 ± 49.7). Although there was no relationship between CK and β-hCG level, it was found that the level of CK did not differ according to TVUS findings and gestational age. Our study shows that we cannot benefit from CK levels as a predictor of resolution time for medically treated and a predictor for cases where surgical exploration is possible.

## CONCLUSION

As a result, In patients treated conservatively for ectopic pregnancies, CK levels at the outset neither predict an acute abdomen to emerge nor shed light on the resolution period in patients who respond to medical therapy. We determined that the most effective β-hCG value that could be used to predict acute abdomen was 6486 mIU/mL.

*Authors' Contribution*

Study Conception: OHD; Study Design: OHD; Supervision: OHD; Funding: SRO; Materials: SRO; Data Collection and/or Processing: SRO; Statistical Analysis and/or Data Interpretation: SRO, OHD; Literature Review: SRO; Manuscript Preparation: SRO and Critical Review: SRO, OHD.

*Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

*Financing*

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# Predictive value of calculated plasma osmolality and atherogenic index of plasma for chronic limb-threatening ischemia in lower extremity artery disease

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## ABSTRACT

**Objectives:** Chronic limb-threatening ischemia (CLTI) is the end-stage form of lower extremity artery disease (LEAD) whose main reason is atherosclerosis. Plasma osmolality (PO) and plasma lipid levels affect the development and progression of atherosclerosis directly. The purpose of this study was to investigate the predictive effect of PO and atherogenic index of plasma (AIP) for the development of CLTI.

**Methods:** A total of 324 patients who were diagnosed with LEAD were analyzed retrospectively. The clinical stage of the disease was evaluated according to the Rutherford classification, and patients without CLTI were defined as "Group 1" and patients with CLTI as "Group 2".

**Results:** There were 248 patients (mean age 64.44 ± 9.05 years and 73.4% male) in Group 1, and 76 patients (mean age 66.62 ± 8.22 years and 76.3% male) in Group 2. In the multivariate regression analysis, CAD, PO, CRP and AIP were defined as independent predictive factors for the development of CLTI ($p = 0.015$, $p < 0.001$, $p = 0.007$, $p < 0.001$; respectively). ROC curve analysis showed that, PO cut-off value for CLTI development was 293.28 mOsm/kg (AUC: 0.821, $p < 0.001$) with 75% sensitivity and 74.2% specificity, and AIP cut-off value was 0.23 (AUC: 0.740, $p < 0.001$) with 67.1% sensitivity and 68.5% specificity.

**Conclusions:** The PO and AIP values in LEAD patients may be used as the new biomarkers of atherosclerosis progression, and therefore as predictive factors for the development of CLTI.

**Keywords:** Atherogenic index of plasma, chronic limb-threatening ischemia, osmolality, lower extremity artery disease

Peripheral artery disease (PAD) is a common disease with its main cause as atherosclerosis. Globally, more than 200 million adults live with PAD. PAD is more common in men and its incidence is increasing, especially in women over the age of 50. The most significant risk factors identified for PAD are diabetes mellitus, hypertension, hyperlipidemia, chronic renal disease and smoking [1, 2]. Lower extremity artery disease (LEAD) affects the lower extremity arteries and although it is mostly asymptomatic, patients often present with a hospital admission of intermittent claudication. The end-stage form of LEAD associated with high mortality and morbidity is chronic limb-threatening ischemia (CLTI). The diagnosis of CLTI is made clinically, and is characterized by ischemic resting pain, ulcerations and gangrene as a result of arterial blood flow insufficiency due to atherosclerosis progression [3].

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Plasma osmolality (PO) is associated with the amount of minerals and particles dissolved in the blood. Since it is accepted as an indicator of body hydration, and since it affects endothelial cells, it has been associated with the prognosis of diseases [4, 5]. Fasting blood glucose, sodium (Na) and blood urea nitrogen (BUN) are the main components of PO; and seperate studies were conducted previously on the effects of each one on vascular diseases [6-8]. However, there are no studies in the literature regarding the effect of changes in PO calculated from these components on LEAD.

After understanding the role of plasma lipids in the pathogenesis of atherosclerosis, studies have been conducted to investigate the relationships between lipid profiles and LEAD. Low levels of high-density lipoprotein cholesterol (HDL-C) are among the strongest plasma lipid risk factors for LEAD. There is a relationship between triglyceride (TG) levels and LEAD progression [9]. In the Framingham Offspring Study, increased TG levels and decreased HDL-C levels were associated with increased LEAD risk [10]. In recent years, atherogenic index of plasma (AIP) has been identified as a new predictor of atherosclerosis. AIP is calculated with the logarithmic transformation of TG/HDL-C ratio [11]. Based on this information, we established the hypothesis that AIP could be a powerful biomarker for the development of CLTI.

It is important to know the predictors of CLTI development in patients diagnosed with LEAD, to detect them earlier, and to plan the treatment strategy early for these patients. For this reason, the purpose of this study was to investigate the relation between the development of CLTI and PO values and AIP values to predict the progression of atherosclerosis in patients with LEAD diagnosis, and to contribute to the preventability of atherosclerosis progression with more effective treatment and follow-up.

## METHODS

A total of 324 patients diagnosed with LEAD between January 2018 and June 2020 admitting to our outpatient clinic were included in this study retrospectively, and study approved by local ethics committee (Adıyaman University Clinical Research Ethics Committee, 21.07.2020, 2020/7-3). The patient data were found from the patient files and the hospital registration system.

The LEAD diagnosis in our outpatient clinic is made with clinical examination of patients, ankle brachial systolic pressure index (ABI) measurement and color doppler ultrasonography [12]. Clinical stage evaluation of the disease is done according to the Rutherford classification. In the Rutherford Classification, asymptomatic patients are expressed as “Category 0”, mild claudication presence is expressed as “Category 1”, moderate claudication presence is expressed as “Category 2”, severe claudication presence is expressed as “Category 3”, presence of ischemic rest pain is expressed as “Category 4”, presence of minor tissue loss presence is expressed as “Category 5”, presence of major tissue loss is expressed as “Category 6” [13]. In recent years, "CLTI" definition has been used for category 4 and above in the Rutherford classification [3].

The patients who had a history of surgical or endovascular intervention with a diagnosis of LEAD, patients with acute limb ischemia, patients with diabetes mellitus diagnosis and using antidiabetic drugs, patients with chronic liver or renal disease, patients with known malignancy or systemic inflammatory disease, patients using steroid or statin group drug and patients with familial hyperlipidemia were excluded from the study. After applying these exclusion criteria, patients diagnosed with LEAD and in categories 0, 1, 2 and 3 according to the Rutherford classification were included in the study as "Group 1"; and the patients in categories 4, 5 and 6, that is, those who developed CLTI, were included in the study as "Group 2". The demographic data, comorbidities, and routine blood tests of the patients were evaluated.

### Laboratory analysis and calculation of PO and AIP

The venous blood samples of patients diagnosed with LEAD were evaluated after 12 hours of fasting by taking blood from the antecubital vein into EDTA (ethylenediaminetetraacetic acid) tubes. The automatic analyzer (Abbott CELL-DYN Ruby; Illinois, USA) was used for complete blood count. Fasting blood glucose, creatinine, BUN, Na, HDL-C, TG, low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and C-reactive protein (CRP) levels were analyzed with (Abbott 16000; Illinois, USA) automatic analyzer.

The following formula was used to calculate the

PO: Osmolality = (BUN / 2.8) + (Glucose / 18) + (2 × Na). And the normal PO value range was described as 275 - 295 mOsm/kg [14].

The following formula was used to calculate the AIP: AIP = log10 (TG / HDL-C). In this calculation, concentrations are expressed in mmol/L [11].

## Statistical Analysis

The data were analyzed with SPSS 11.5 Program. As descriptive, mean ± standard deviation and median (minimum-maximum) values were used for quantitative variables, and number of patients (percent) was used for qualitative variables. Shapiro-Wilk test was used to test the normality distribution of the data. In terms of the quantitative variable, the difference between the two categories of qualitative variable categories was checked by Student-t test if the normal distribution assumptions were met; and if not by Mann-Whitney U test. When wanted to examine the relation between qualitative variables, the Chi-Square test was used. The Receiver Operating Characteristic (ROC) analysis was performed to find a method for determining the development of CLTI for the quantitative variable. The cut-off value for the quantitative variable was determined with the Youden Index. The univariate logistic regression and multivariate logistic

**Table 1. Comparison of clinical and demographic characteristics of patient groups**

| Variables | | Group 1 (n = 248) | | Group 2 (n = 76) | | *p* value |
|---|---|---|---|---|---|---|
| | | Mean ± SD / n (%) | Median (Min-Max) | Mean ± SD / n (%) | Median (Min-Max) | |
| Age (years) | | 64.44 ± 9.05 | 65.00 (44.00-86.00) | 66.62 ± 8.22 | 67.00 (45.00-85.00) | 0.061[a] |
| Gender | Male | 182 (73.4%) | | 58 (76.3%) | | 0.610[c] |
| | Female | 66 (26.6%) | | 18 (23.7%) | | |
| BMI (kg/m$^2$) | | 25.84 ± 3.47 | 25.80 (18.60-34.60) | 26.07 ± 2.63 | 26.40 (19.40-33.10) | 0.542[a] |
| Hypertension | | 167 (67.3%) | | 54 (71.1%) | | 0.543[c] |
| CAD | | 106 (42.7%) | | 47 (61.8%) | | **0.004[c]** |
| Atrial fibrillation | | 41 (16.5%) | | 13 (17.1%) | | 0.907[c] |
| CVD | | 74 (29.8%) | | 28 (36.8%) | | 0.250[c] |
| Current smoking | | 127 (51.2%) | | 43 (56.6%) | | 0.412[c] |
| COPD | | 55 (22.2%) | | 18 (23.7%) | | 0.783[c] |
| ABI | | 0.59 ± 0.12 | 0.57 (0.43-0.89) | 0.36 ± 0.07 | 0.37 (0.19-0.48) | **< 0.001[a]** |
| Rutherford category | | | | | | |
| | 0 | 23 (9.3%) | | 0 | | **< 0.001[c]** |
| | 1 | 73 (29.4%) | | 0 | | |
| | 2 | 89 (35.9%) | | 0 | | |
| | 3 | 63 (25.4%) | | 0 | | |
| | 4 | 0 | | 37 (48.7%) | | |
| | 5 | 0 | | 28 (36.8%) | | |
| | 6 | 0 | | 11 (14.5%) | | |

SD = Standard deviation, Min = Minimum, Max =Maximum; [a]Student-t test, [c]Chi-square test, BMI = Body mass index, CAD = Coronary artery disease, CVD = Cerebrovascular disease, COPD = Chronic obstructive pulmonary disease, ABI = Ankle brachial index

**Table 2. Comparison of laboratory variables of patient groups**

| Variables | Group 1 (n = 248) | | Group 2 (n = 76) | | *p* value |
|---|---|---|---|---|---|
| | Mean ± SD / n (%) | Median (Min-Max) | Mean ± SD / n (%) | Median (Min-Max) | |
| Fasting blood glucose (mg/dL) | 112.68 ± 23.95 | 112.00 (65.00-193.00) | 121.97 ± 24.30 | 120.00 (74.00-182.00) | 0.003[a] |
| Creatinine (mg/dL) | 0.91 ± 0.30 | 0.86 (0.50-2.38) | 0.90 ± 0.21 | 0.93 (0.70-2.21) | 0.423[b] |
| Blood urea nitrogen (mg/dL) | 20.96 ± 5.35 | 20.00 (11.00-37.00) | 24.79 ± 6.94 | 24.50 (14.00-42.00) | < 0.001[a] |
| Sodium (mEq/L) | 137.31 ± 3.22 | 137.00 (129.00-147.00) | 140.91 ± 2.92 | 141.00 (133.00-145.00) | < 0.001[a] |
| PO (mOsm/kg) | 288.36 ± 7.22 | 287.36 (272.38-312.54) | 297.45 ± 6.78 | 297.32 (280.37-311.94) | < 0.001[a] |
| TC (mmol/L) | 5.19 ± 0.61 | 5.28 (3.58-6.50) | 5.16 ± 0.67 | 5.26 (3.65-6.72) | 0.694[a] |
| TG (mmol/L) | 1.66 ± 0.41 | 1.67 (0.78-2.89) | 1.83 ± 0.42 | 1.85 (0.91-2.81) | 0.002[a] |
| HDL-C (mmol/L) | 1.13 ± 0.16 | 1.16 (0.80-1.45) | 0.96 ± 0.10 | 0.93 (0.80-1.19) | < 0.001[a] |
| LDL-C (mmol/L) | 3.29 ± 0.55 | 3.41 (2.02-4.40) | 3.36 ± 0.58 | 3.48 (2.04-4.73) | 0.372[a] |
| AIP | 0.16 ± 0.14 | 0.17 (-0.26-0.55) | 0.27 ± 0.11 | 0.28 (-0.02-0.54) | < 0.001[b] |
| C-reactive protein (mg/dL) | 4.77 ± 2.95 | 3.56 (0.70-13.70) | 5.84 ± 3.18 | 5.01 (1.02-12.80) | 0.005[b] |
| Hemoglobin (g/dL) | 13.34 ± 1.77 | 13.50 (9.20-16.90) | 12.95 ± 1.80 | 12.75 (9.80-17.40) | 0.094[a] |
| White blood cell (103/µL) | 8.57 ± 2.26 | 8.42 (4.89-14.12) | 8.84 ± 2.19 | 8.57 (5.14-14.85) | 0.361[a] |
| Platelet (103/µL) | 247.01 ± 64.69 | 238.50 (104.00-496.00) | 237.34 ± 67.85 | 224.00 (129.00-479.00) | 0.149[b] |
| Mean platelet volume (fL) | 8.83 ± 1.18 | 8.77 (6.45-11.24) | 9.27 ± 1.30 | 9.53 (6.26-11.35) | 0.006[a] |

SD = Standard deviation, Min = Minimum, Max =Maximum; [a]Student-t test, [b]Mann-Whitney U test, PO = Plasma osmolality, TC = Total cholesterol, TG = Triglyceride, HDL-C = High-density lipoprotein cholesterol, LDL-C = Low-density lipoprotein cholesterol, AIP = Atherogenic index of plasma

regression analyzes were performed to show risk factors for CLTI development. Statistical significance level was accepted as $p < 0.05$.

## RESULTS

This study included 324 patients diagnosed with LEAD. There were 248 patients in Group 1 (mean age 64.44 ± 9.05 years; 73.4% male) and 76 patients in Group 2 (mean age 66.62 ± 8.22 years; 76.3% male). The mean ABI measurement of patients in Group 1 was 0.59 ± 0.11; and that of patients in Group 2 was 0.36 ± 0.08 ($p < 0.001$). No significant difference was found between the patient groups in terms of gender, age, body mass index, hypertension, atrial fibrillation, cerebrovascular disease, current smoking status, and chronic obstructive pulmonary disease. Patients in Group 2 had significantly higher concomitant coronary artery disease (CAD) compared to Group 1 (61.8% vs 42.7%, $p = 0.004$). The clinical and demographic characteristics of the patient groups are shown in Table 1.

When the laboratory variables of patient groups were compared, it was found that the values of Na, BUN, fasting blood glucose and PO were significantly higher in Group 2 ($p < 0.001$, $p < 0.001$, $p = 0.003$, $p < 0.001$; respectively). HDL-C value, which is one of the lipid profile variables, was significantly lower in Group 2, while TG and AIP values were found to be high ($p < 0.001$, $p = 0.002$, $p < 0.001$; respectively). CRP and mean platelet volume (MPV) values were also found to be significantly higher in Group 2 ($p = 0.005$, $p = 0.006$; respectively) (Table 2).

When the results of univariate logistic regression analysis that was done to determine possible predictors of the development of CLTI were evaluated, CAD, PO, AIP, MPV and CRP variables were found to be significant risk factors, and these variables were included in the multivariate analysis (Table 3). And according to this analysis, CAD, PO, CRP and AIP variables were found to be independent predictive factors for the development of CLTI ($p = 0.015$, $p < 0.001$, $p = 0.007$, $p < 0.001$; respectively).

To determine the predictive effect of PO and AIP levels in the development of CLTI, ROC Curve analysis was done. The ideal cut-off value for calculated PO was 293.28 mOsm/kg (Area Under the Curve [AUC]: 0.821, $p < 0.001$) with 75% sensitivity and 74.2% specificity. The ideal cut-off value for AIP was 0.23 (AUC: 0.740, $p < 0.001$) with 67.1% sensitivity and 68.5% specificity (Fig. 1).

## DISCUSSION

The relation between CLTI development and calculated PO values and AIP values was investigated in

**Table 3. Univariate and multivariate logistic regression analysis to determine predictors of the development of chronic limb-threatening ischemia**

| Variables | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | *p* value | OR | 95% CI Lower-Upper | *p* value | OR | 95% CI Lower-Upper |
| Age | 0.062 | 1.028 | 0.999-1.059 | | | |
| Gender (Male) | 0.610 | 1.168 | 0.642-2.127 | | | |
| CAD | **0.004** | 2.171 | 1.282-3.677 | **0.015** | 2.245 | 1.171-4.304 |
| Smoking | 0.413 | 1.241 | 0.740-2.083 | | | |
| PO | **< 0.001** | 1.182 | 1.131-1.236 | **< 0.001** | 1.168 | 1.114-1.225 |
| AIP | **< 0.001** | 1406.004 | 120.477-16408.483 | **< 0.001** | 735.730 | 41.043-1188.634 |
| CRP | **0.008** | 1.115 | 1.028-1.208 | **0.007** | 1.156 | 1.040-1.285 |
| MPV | **0.007** | 1.352 | 1.087-1.680 | | | |

OR = Odds ratio, CI = Confidence interval, CAD = Coronary artery disease, PO = Plasma osmolality, AIP = Atherogenic index of plasma, CRP = C-Reactive protein, MPV = Mean platelet volume

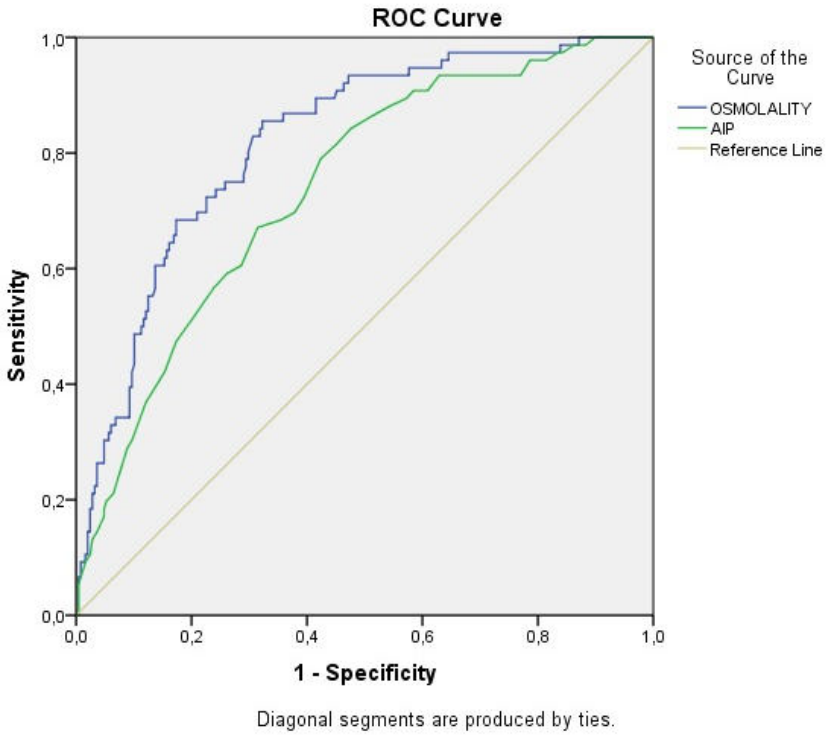


**Fig. 1. ROC curve of calculated PO and AIP for predicting the development of chronic limb-threatening ischemia.**

this retrospective study. We found that the increase in PO values and AIP values was related with the development of CLTI in patients with LEAD. In the multivariate logistic regression analysis, CAD, CRP, PO and AIP variables were found as independent predictive factors for CLTI development. In patients with LEAD diagnosis, it was found that having concomitant CAD increased the risk of developing CLTI by 2.245 times, one unit increase in CRP quantitative variable increased the risk of developing CLTI by 1.156 times, one unit increase of PO quantitative variable increased the risk of developing CLTI by 1.168 times, and 0.1 unit increase in AIP quantitative variable increased the risk of developing CLTI by 1.935 times. To the best of our knowledge, we determined for the first time in the literature with this study that the development of CLTI can be predicted with PO values and AIP values in patients with LEAD diagnosis.

CLTI is the end-stage of LEAD, and is related with high morbidity and mortality. It was reported that, major amputation rate was 30% and mortality rate was 25% in patients within 1 year after the development of CLTI [15]. Therefore, it is important to plan the treatment of LEAD patients before CLTI develops. In addition to medical treatments (antithrombotic, lipid-lowering, antihypertensive agents) and treatment approaches such as exercise, diet, smoking cessation, and preventive foot care applied in symptomatic LEAD patients, early revascularization options are also recommended for patients at high risk of developing CLTI [1, 3]. In recent years, many predictors of CLTI development have been identified in patients diagnosed with LEAD [16, 17]. Since atherosclerosis is the underlying cause of LEAD pathology, the identified predictors are focused on atherosclerosis, which is considered an inflammatory process.

Atherosclerosis is multifactorial and inflammation plays an important role in its patagonesis from its development to its progression. Plasma osmolality can be defined as the solite load in the body, and indicates body hydration. The increase in PO increases the inflammation and atherosclerosis progression in vascular endothelial cells by increasing the hemoconcentration [18, 19]. In their study of 315 patients, Rasouli *et al*. [4] reported that calculated PO, which is one of the markers of dehydration and hemoconcentration, showed correlations with CAD severity. In a study on 3748 acute coronary syndrome patients conducted by Tatlisu *et al*. [20], it was reported that PO at admission could be used to identify high-risk patients and is a predictor of in-hospital and long-term

mortality. Similar to these studies in the literature, statistically significant high PO values were found in patients who developed CLTI in our study ($p < 0.001$). In addition, PO has been found to be an independent predictor of CLTI development (odds ratio (OR): 1.168, 95% confidence interval (CI): 1.114-1.225, $p < 0.001$). It is known that diabetes mellitus is an important risk factor in LEAD etiology, increasing the risk of LEAD development by three-four times. It also accelerates the development of CLTI by increasing vascular inflammation and delaying the diagnosis and treatment of the disease with peripheral neuropathy effect [15]. In addition, since diabetes mellitus would increase PO alone, and reduce the reliability of the results of our study; patients with diabetes mellitus diagnosis and using antidiabetic drugs were not included in the study. Also, patients with chronic renal disease, which has close relations with atherosclerosis progression, and which might change PO with direct effect on plasma electrolyte values, were also excluded from the study [21].

Dyslipidemia causes the development and progression of atherosclerosis by affecting vascular endothelial cells. High TC and LDL-C levels are considered to be risk factors for LEAD, and low HDL-C levels were significantly associated with increased mortality and other cardiovascular complications in LEAD patients [22, 23]. Small dense LDL-C is the subfraction of LDL-C with high atherogenic potential, and increases in direct proportion with TG levels. For this reason, there is a strong relation between the increase in TG levels and atherosclerotic diseases [24]. Recently, AIP, which is calculated with the logarithmic transformation of plasma TG and HDL-C molar levels, has been described as a novel and powerful clinical biomarker for atherosclerotic diseases [11, 25]. In their prospective studies in which 2676 middle-aged individuals were included with a follow-up period of 7.8 years, Onat *et al*. [26] reported that AIP variable was an independent predictive factor for CAD. In the case-control study of 696 individuals conducted by Wu *et al*. [27], AIP was reported to be a strong predictive biomarker for CAD risk in women (OR: 3.290, 95% CI: 1.842-5.877, $p < 0.001$). In a meta-analysis summarizing the data related to AIP calculated in 8394 individuals, it was reported that the values -0.3 to 0.1 were associated with low, 0.1 to 0.24 were associated with medium and above 0.24 were associated with high cardiovascular disease risk [28]. In our study, which included patients with LEAD diagnosis, statistically significant high AIP values were detected in patient group with CLTI, and AIP was detected as an independent predictive factor for CLTI development. The ideal AIP cut-off value for CLTI development was found as 0.23 with 67.1% sensitivity and 68.5% specificity.

In our study, statistically significant low HDL-C levels and high CRP levels were noted in patient group with CLTI ($p < 0.001$, $p = 0.005$; respectively). HDL-C is known as antiatherogenic lipoprotein due to its reverse cholesterol transport properties. Additionally, it has antioxidant and anti-inflammatory properties, and in particular, it inhibits vascular inflammation by inhibiting the expression of adhesion molecules from endothelial cells. For this reason, there is a negative correlation between HDL-C and CRP, which are inflammatory biomarkers [23]. It was also shown that there is a relation between elevation in CRP levels and the severity of atherosclerosis and LEAD [1]. Swastini *et al*. [29] investigated the relationship between CRP and atherosclerosis severity measured by ABI and doppler ultrasonography in 388 patients with dyslipidemia. They published that there was a important correlation between CRP levels and the severity of atherosclerosis. Barani *et al*. [30] associated CRP levels with 1-year mortality in CLTI patients. Based on our findings, we found that the CRP level is an independent predictive factor for CLTI development (OR: 1.156, 95% CI: 1.040-1.285, $p = 0.007$).

Atherosclerosis is a systemic disease, affecting many arteries simultaneously. Patients with LEAD diagnosis have concomitant CAD at a rate between 40% and 55% [15, 31]. It has been reported that the presence of CAD is an independent risk factor for mortality [32]. A total of 47.2% of the patients who were included in our study had concomitant CAD, and there were significantly higher CAD in patient group with CLTI. It was found that concomitant CAD in LEAD patients is an independent predictive factor for CLTI development (OR: 2.245, 95% CI: 1.171-4.304, $p = 0.015$).

## Limitations

Our study had several limitations to consider. First of all, our study was single-centered, and was designed retrospectively. Patients who were diagnosed with

LEAD, that is, mostly symptomatic, with outpatient clinic application were included in our study. The rate of presence of symptoms in LEAD patients is 35% [33]. For this reason, studies that involve wider patient populations, including asymptomatic LEAD patients, should be planned to ensure that these two laboratory parameters we calculated to enter clinical use. In addition, stating the smoking status as only current smokers, not as pack years or former smokers, can be considered as another limitation of our study.

## CONCLUSION

According to the data of our study, it was found that PO values and AIP values that are calculated simply from routine biochemical tests in patients with LEAD diagnosis were associated with the development of CLTI. Our analysis showed that CAD, PO, AIP and CRP are independent predictive factors for for CLTI development in patients with LEAD diagnosis. Since these patients may benefit from aggressive management of risk factors and intensified treatment options to prevent CLTI-related morbidity and mortality, we believe that identifying the high-risk population for the development of CLTI in patients with a diagnosis of LEAD is of great importance.

*Authors' Contribution*

Study Conception: AAP; Study Design: AAP, YSU; Supervision: AAP; Funding: AAP; Materials: AAP; Data Collection and/or Processing: AAP, YSU; Statistical Analysis and/or Data Interpretation: AAP, YSU; Literature Review: AAP; Manuscript Preparation: AAP and Critical Review: AAP, YSU.

*Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

*Financing*

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# A clue for obstructive sleep apnea hidden in tomographic images of idiopathic pulmonary fibrosis patients

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## ABSTRACT

**Objectives:** The most common opinion about apnea/hypopnea formation in restrictive pulmonary diseases is based on decreased lung volumes causing upper airway collapse. This study targets to reveal some evidence for this pathophysiological pathway in patients with idiopathic pulmonary fibrosis (IPF) and obstructive sleep apnea (OSA).

**Methods:** The clinical, demographical, and polysomnographic characteristics of 19 patients with OSA and IPF who underwent all-night polysomnography (PSG) were retrospectively evaluated for investigating the correlations between lung volumes calculated on the images of high-resolution computed tomography (HRCT) and polysomnographic findings. Supine HRCT images performed at the time of diagnosis of IPF were used for the calculation of total lung volume and low attenuation areas of the lung (LAA). The results were compared with the results of the PSG and pulmonary function tests (PFT).

**Results:** The study group comprised 19 patients (3 female, 16 male) with a median apnea-hypopnea index (AHI) of 23.5/h. AHI in this IPF cohort was not correlated with body-mass index, neck circumference, age, or PFT. However, overall AHI and non-rapid eye movement (non-REM) AHI had a trend of positive correlation with LAA. We also showed a positive correlation between the LAA and forced vital capacity (FVC) ($r = 0.682$ and, $p = 0.003$).

**Conclusions:** The severity of OSAS in IPF patients is well correlated with LAA. This result supports the gravitational and the volumetric effect of the lung in apnea-hypopnea formation.

**Keywords:** idiopathic pulmonary fibrosis; low attenuation areas of the lung; obstructive sleep apnea; pulmonary function tests; quantitative imaging

Obstructive sleep apnea syndrome (OSAS) was defined as one of the comorbidities of idiopathic pulmonary fibrosis (IPF) which is the most common type of idiopathic interstitial pneumonia [1]. Sleep disorders accompanying obstructive or restrictive lung diseases were classified under 'Sleep-Related Hypoventilation/Hypoxemia Due to Medical Condition' in the "International classification of sleep disorders-3" which was published in 2014 [2]. Rather than being a coincidence, OSAS and IPF may have a role in the pathogenesis of each other. Gastroesophageal reflux disease, oxidative distress, and nocturnal desaturations are seen in OSAS may cause alveolar damage leading to IPF [3]. Mutually, the reduction of lung volumes in

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IPF facilitates apnea/hypopnea formation by increasing the collapsibility of upper airways due to the decrease in the caudal retraction effect of lungs over upper airways [3].

However previous studies investigating the relationship between forced vital capacity (FVC), forced expiratory volume during the first second (FEV1) and severity of OSAS reported conflicting results [4]. The results of the study held by Lancaster *et al*. [5] could not support the previous evidence indicating a negative correlation between pulmonary function tests and apnea-hypopnea index. Pulmonary function tests performed at the sitting position may conceal the real fact of pulmonary function impairment on polysomnography obtained during sleep in the supine position. Therefore, the radiologic calculation of lung volumes by using tomographic images taken in supine position before the treatment can be more informative than conventional pulmonary function tests in uncovering the pathophysiology of OSA in restrictive lung diseases.

This study is conducted to enlighten the correlations between total lung volumes (total lung volume and low attenuation areas of the lung) on high-resolution computed tomography (HRCT) and the severity of OSAS in IPF patients.

## METHODS

### Study Population

The study protocol was approved by the institutional review board of our hospital (decision no: 610 decision date: 02/11/2018). All procedures performed in this study comply with the ethical standards of the institutional review board and with the 1964 Helsinki declaration and its later amendments. We analyzed only records of patients who agreed to the use of their data.

The study group comprises 23 IPF patients who were consecutively referred to sleep disorders center due to clinical suspicion of OSA and underwent all-night polysomnography (PSG) between March 2016 and June 2017. The diagnosis of IPF (either radiological or pathological) was based on the final decision of the multidisciplinary council for interstitial lung diseases at our hospital as recommended in the available guideline published for the diagnosis of IPF [1]. Medical records of 23 patients were retrospectively evaluated. OSA was defined as an apnea-hypopnea index (AHI) of ≥ 5 events/h on PSG [2]. Out of 23 patients who were polysomnographically diagnosed as OSAS, one patient with congestive heart failure and three patients whose HRCT scans were not available were excluded. The remaining 19 patients were sleep-modifying drugs free and at the time of the computed tomography (CT) scan, either corticosteroids or antifibrotic drugs had not been initiated yet. The patients did not have any comorbidity like cerebrovascular diseases or obstructive lung diseases, which could affect the results of the study.

A pulmonary function test (PFT) was performed for all capable patients. Measurements including spirometry (n = 17) and diffusing capacity of the lung for carbon monoxide divided by the alveolar volume (DLCO/VA) (n = 12) by the single breath technique were performed according to current guidelines, in the seated position [6].

Age, gender, body mass index (BMI), symptoms, neck circumference (NC), smoking status, and scores on the Epworth Sleepiness Scale (ESS) and the results of PSG were obtained from the medical records of the remaining 19 patients.

### Polysomnography

PSG including four channels of electroencephalography, two channels of electrooculography, one channel of chin electromyography, thermistor and nasal pressure transducer monitoring to measure airflow, thoracic and abdominal wall motion monitoring to measure respiratory effort, pulse oximetry to measure oxygen saturation, electrocardiography, and a microphone to record snoring was performed using a digital system (Neuron-Spectrum EEG and EP neurophysiological system version 1.6.9.6, Neurosoft, Russia). The records were manually scored based on the criteria of the American Academy of Sleep Medicine (AASM) Scoring Manual Version 2.2 by a sleep specialist [7].

### High-Resolution Computed Tomography Imaging

HRCT examinations were performed in the supine position and deep inspiration by using Siemens Emotion 6 (Siemens AG, Erlangen, Germany) and Toshiba Alexion 16 (Nasu, Japan) for the diagnosis of IPF. No contrast medium was injected. CT images were re-

viewed by using the picture archiving and communication system (PACS). Parameters were each set to 80-135kV, 50-300 mA with dose modulation, a 1 mm and -1.25 mm thickness, and reconstruction. All axial and reconstructed CT images were reviewed in the PACS by using mediastinal (width, 340 HU; level, 50 HU) and lung (width, 1500 HU; level, −500/-600 HU) window settings. After CT scanning, images were reconstructed by using a pre-installed post-processing program (General Electric GEAW Server 3.2 Thoracic VCAR). Thoracic VCAR is a non-invasive CT image analysis software package, by which areas of the lung with a preset value of Hounsfield Units (HU) can be determined in conjunction with CT lung images. These areas are shown color (blue) for the assessment of the lung diseases [8]. The percentage and volume of low attenuation areas of the lung (LAA) were calculated by the density mask method which was set to show lung voxels with a density lower than 950 HU [9]. (Fig. 1) Total lung volume (TLV), which was reported by this software was also analyzed.

### Statistical Analysis

Data were analyzed using SPSS for Windows 15 software. Normality for the continuous variables was analyzed using the Shapiro-Wilk test. Descriptive statistics were presented as mean ± standard deviation for the normally distributed variables and median (minimum-maximum) for randomly distributed variables. Nominal variables were presented as the number and percentage of cases. Most of the variables were randomly distributed and the study comprised a small number of patients. Hence, the Spearman correlation coefficient (r) was employed to examine the relationship between lung volumes and results of PSG, demographic characteristics, or PFT. A multiple linear regression model was used to identify the predictive value of LAA (L) and BMI for AHI. Before the analysis, the logarithmic transformation of the non-normally distributed data was performed to obtain a normal distribution. The model fit was assessed using appropriate residual and goodness-of-fit statistics. *P*-value < 0.05 was considered as statistically significant.

## RESULTS

Out of 23 patients with IPF whose PSG results revealed accompanying OSAS, 19 patients (3 female, 16 male) were included in the analysis. The baseline

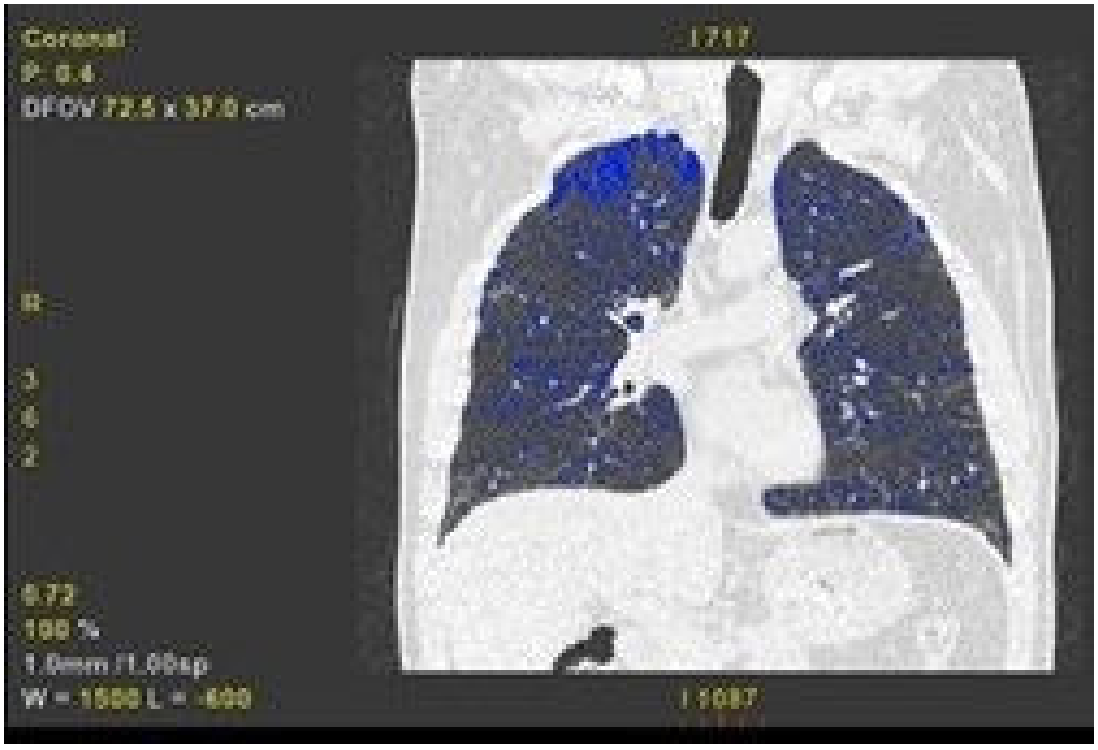


**Fig. 1. Representative HRCT scan of a patient. A male patient, 56 years old. The percentage of low attenuation areas (shown as blue) was 10.2%.**

characteristics of the study subjects were shown in Table 1. Most patients had moderate/severe OSAS (n = 16, 84.2%) and the median AHI was 23.5/h. The details of PSG results were represented in Table 2. It was found that an averagely of 89.1% of respiratory events comprised hypopneas.

The correlation coefficients (r values) between the parameters of PSG and demographic characteristics, pulmonary function tests, or quantitative CT results were shown in Table 3. Correlation analysis showed that age was positively correlated with nREM1% ($p$ = 0.019 and r = 0.531). The amount of smoking (packages/year) was correlated negatively with REM% (r = -0.657) and the percentage of slow-wave sleep (nREM3%) (r = -0.728) and positively with nREM1% (r = 0.858), nREM2% (r = -0.728) ($p < 0.05$). The ratio of FEV1/FVC had a positive correlation with REM% and nREM3% (r = 0.523 and, r = 0.610, respectively).

**Table1. Clinical and demographical characteristics of the patients**

| | **(n = 19)<br>mean ± SD<br>median (25th -75th percentile)<br>n (%)** |
|---|---|
| **Age** | 66.4 ± 9.4 |
| **Gender** | |
| Female | 3 (15.8%) |
| Male | 16 (84.2%) |
| **BMI** | 26.7 ± 3.7 |
| **Smoking status** | |
| none smoker | 6 (31.6%) |
| quitted/active smoker | 13 (68.4%) |
| **Smoking (packages/year)** | 45 (20-55) |
| Diagnosis | |
| Clinical-radiological | 15 (78.9%) |
| VATS | 3 (15.8%) |
| Open lung biopsy | 1 (5.3%) |
| **PFT (n = 17)** | |
| FVC | 2.4 ± 0.85 |
| FVC (%) | 69.7 ± 19.6 |
| FEV1 | 1.6 (1.42-2.62) |
| FEV1 (%) | 73.6 ± 21.8 |
| FEV1/FVC | 83.2 ± 8.8 |
| **DLCO (%) (n = 10)** | 51.5 (24.5-82.8) |
| **DLCO/VA (%) (n = 12)** | 79.7 ± 39.9 |
| **Neck circumference (cm)** | 38.8 (37.5–41) |
| **ESS (n = 17)** | 4 (2-6,5) |
| **Total lung volume (L)** | 3.37 ± 1.38 |
| **LAA (L)** | 0.22 (0.16-0.65) |
| **LAA (%)** | 9.2 (6.2-15.4) |

BMI = body mass index, DLCO/VA = diffusing capacity divided by the alveolar volume, ESS = Epworth Sleepiness Scale, FVC = forced vital capacity, FEV1 = forced expiratory volume during the first second, LAA = low-attenuation areas of the lungs PFT = pulmonary function test, VATS = Video-assisted thoracoscopic surgery

**Table 2.** **Polysomnographic characteristics**

| | mean ± SD<br>median ($25^{th}$-$75^{th}$ percentile)<br>n (%) |
|---|---|
| TST (min) | 321.9 ± 70.3 |
| Sleep efficiency (%) | 66.0 ± 14 |
| REM sleep (%) | 11.5 ± 5.7 |
| nREM1 (%) | 9.6 ± 5.6 |
| nREM2 (%) | 59.3 ±14.1 |
| nREM3 (%) | 17.3 (5.8-27.3) |
| AHI | 23.5 (16.6-43.4) |

AHI = apnoea-hypopnea index, REM = rapid eye movement, TST = total sleep time

**Table 3.** **Correlations between polysomnographic and clinical/radiological variables**

| Variables | LAA (L) | | LAA (%) | |
|---|---|---|---|---|
| | r | *p* value | r | *p* value |
| Age | 0.156 | 0.523 | 0.272 | 0.229 |
| BMI (n = 18) | -0.173 | 0.494 | -0.208 | 0.408 |
| Smoking (pack year) (n = 13) | 0.646 | 0.017 | 0.623 | 0.023 |
| FVC (L) (n = 17) | 0.682 | 0.003 | 0.587 | 0.013 |
| FEV1 (L) (n = 17) | 0.527 | 0.03 | 0.477 | 0.053 |
| FVC (%) (n = 17) | 0.466 | 0.06 | 0.434 | 0.082 |
| FEV1 (%) (n = 17) | 0.378 | 0.135 | 0.352 | 0.166 |
| FEV1/FVC (n = 17) | -0.583 | 0.014 | 0.538 | 0.026 |
| DLCO (%) (n = 10) | -0.179 | 0.558 | -0.16 | 0.602 |
| DLCO/VA (%) (n = 12) | -0.203 | 0.527 | -0.189 | 0.556 |
| NC (cm) | 0.174 | 0.477 | 0.075 | 0.761 |
| ESS (n = 17) | -0.009 | 0.974 | 0.048 | 0.855 |
| TLV (L) | -0.184 | 0.45 | 0.166 | 0.497 |
| Sleep efficiency | -0.161 | 0.509 | -0.108 | 0.66 |
| REM % | -0.311 | 0.195 | -0.423 | 0.071 |
| NREM 1% | 0.518 | 0.023 | 0.477 | 0.039 |
| NREM 2% | 0.503 | 0.028 | 0.514 | 0.024 |
| NREM 3% | -0.652 | 0.002 | -0.574 | 0.01 |
| AHI | 0.543 | 0.016 | 0.526 | 0.021 |
| ODI | 0.445 | 0.064 | 0.457 | 0.056 |

*r values represent correlation coefficients. BMI = body mass index, DLCO = diffusing capacity of the lungs for carbon monoxide, DLCO/VA = diffusing capacity divided by the alveolar volume, ESS = Epworth Sleepiness Scale, FVC = forced vital capacity, FEV1 = forced expiratory volume during the first second, NC = neck circumference, LAA = low-attenuation areas of the lungs, REM = rapid eye movement, TLV = total lung volume

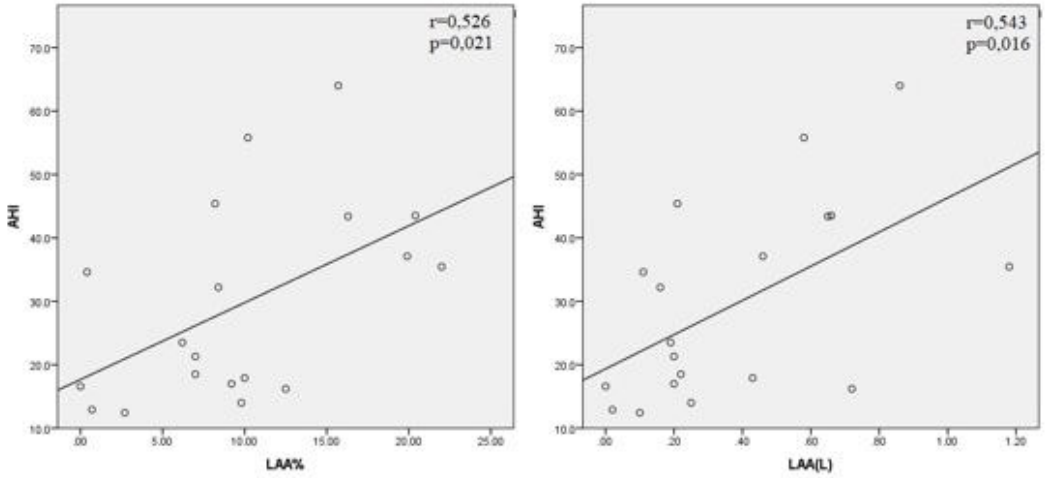


**Fig. 2. a) Relationship between AHI and LAA%, b) Relationship between AHI and LAA(L). AHI = apnea-hypopnea index, LAA = low-attenuation areas of the lungs**

DLCO or DLCO/VA was not correlated with any of the variables. There was a weak positive correlation between ESS scores and nREM1% (r = 0.498). Total lung volume was negatively correlated with the percentage of slow-wave sleep.

Any of the classical predictors of OSAS including BMI, neck circumference, age, pulmonary function tests, or radiologically calculated TLV did not demonstrate a correlation with AHI ($p > 0.05$). However, as shown in Fig. 2, the results indicated that AHI was positively correlated with LAA% and LAA (L) ($p = 0.016$, r = 0.526 and, $p = 0.021$, r = 0.543, respectively). After obtaining normal distribution for LAA (L) and AHI via logarithmic transformation a multiple linear regression model including log [LAA (L)] and BMI was performed. This analysis proved that log [LAA (L)] can be used to predict log (AHI) for IPF patients, regardless of BMI. As the values were shown in Table 4, log (AHI) can be calculated with this formula: log (AHI) =1.58 + 0.31x log [LAA (L)].

## DISCUSSION

This study shows that LAA has a positive correlation with the severity of OSAS. Additionally, our results present proof for the clinical parameters effecting sleep architecture in patients with IPF.

Prior studies dating back to the mid-1980s pointed out poor sleep quality and oxygen desaturation during sleep in patients with interstitial lung diseases [10, 11]. The first study describing sleep-related disorders in a sole group of patients with IPF demonstrated a decrease in sleep efficiency, slow-wave sleep, and REM sleep with an overall AHI in the moderate range [4]. Likewise, the decrease in REM sleep (%11.5 ± 5.7) in our study group indicates the disruption of sleep architecture in IPF. Due to the increased respiratory

**Table 4. Multivariate regression analysis for AHI**

| variables | B ± SH | | |
|---|---|---|---|
| | constant | | *p* value |
| Log (AHI score) | 1.305 | | |
| BMI (kg/m$^2$) | | 0.011 ± 0.014 | 0.464 |
| Log [(LAA (L)] | | 0.31 ± 0.109 | 0.013 |
| Log [(LAA (L)] | 1.582 | 0.31 ± 0.107 | 0.011 |
| $R^2$:0.385, ***p = 0.033*** | | | |

* p-value for ANOVA test, β±SH = regression coefficient ± standard error

AHI = apnea-hypopnea index, dependent variable=AHI, BMI = body mass index, LAA = low-attenuation areas of the lungs

drive and hypocapnia which were suggested as the conservation mechanisms against apnea formation in IPF, the median AHI was in the moderate range and hypopnea predominant. Our data also showed the negative effect of smoking and age on sleep architecture in IPF patients. Smoking cessation may have a positive effect on sleep quality for IPF patients.

Additionally, our results pointed out a trend of a positive correlation between FEV1/FVC, and slow-wave sleep and REM sleep. Despite this impact of FEV1/FVC on sleep architecture, we could not show any correlations between pulmonary function tests and the severity of OSAS. For the general population age, BMI and NC are commonly accepted as predictors for the severity of OSAS [12, 13]. However, the most common opinion about apnea/hypopnea formation in restrictive pulmonary diseases is based on decreased lung volumes causing upper airway collapse, especially during REM sleep due to a decreased traction on the upper airway [4, 5]. This hypothesis was also supported by an animal study demonstrating that the caudal tracheal traction could decrease upper airway collapsibility by reducing extraluminal tissue pressure in rabbits [13]. Similarly, Mermigkis *et al*. [4] noted impairment in pulmonary function tests as potential predictors of OSA in IPF. However, two years later the contradictory results published by Lancaster *et al*. [5]could not indicate any correlations between spirometry or lung volumes with the AHI. A recent meta-analysis elucidated the influence of body position on PFT of the patients with heart, lung, neuromuscular disease, obesity, or spinal cord injury [14]. As PFT is performed while sitting upright and in the daytime, the results can not reflect the pathogenetic pathway of upper airway collapse in a supine position at night during sleep. The results of our study revealed that supine volumes calculated by quantitative analysis of HRCT scan well-correlated with AHI while conventional PFT, DLCO, and DLCO/VA failed to show any correlations in this group of IPF patients. The last guideline proposed the usage of radiologic findings of HRCT as the key factor for the diagnosis of IPF. The same statement called attention to comorbidities like pulmonary hypertension, gastroesophageal reflux disease, and OSAS for IPF patients [16]. Although the effects of these comorbidities need to be further evaluated, some evidence about the unfavorable effects of OSAS in disease progression and life quality of IPF patients has been published [17, 18].

Besides the visual assessment of CT images, a quantitative method using digital data for calculating lung volumes and low attenuation areas of the lung has become a scientific attraction point recently. This method was recommended for representing macroscopic and microscopic emphysematous changes of the lung in chronic obstructive pulmonary disease (COPD) and asthma [19-21]. It was also proposed as a routine follow-up for chronic pulmonary emphysema patients with low radiation at a level of 25% of the routine [22]. LAA% seems to be correlated with pulmonary function tests in asthma and COPD [20, 21, 23].

Some researchers managed to reach positive results outlining the importance of some novel radiologic findings in the assessment of OSA patients. The evaluation of airway ellipticity, water content around the airway, and fat distributions by magnetic resonance imaging were proposed as quick alternatives for identifying the severity of OSA [24-26]. Additionally, CT images obtained during apneic episodes can be used for defining the level of obstruction [27]. In this study, a different radiologic finding was evaluated in an overlapping situation of OSA and IPF. Our results showed that the lung volumes obtained by software from HRCT scans at the supine position may enlighten the caudal traction hypothesis and expressed the effect of low attenuation areas on the severity of OSA for IPF patients. Hochhegger *et al*. [28] investigated air trapping in patients with IPF and other interstitial lung diseases quantitatively by using automated-software and found that air trapping on CT was a common finding for IPF patients as well. The previous studies indicated that the vertical gradient of lung density in the supine position was less at total lung capacity than at residual volume in healthy people. The vertical gradient of an emphysematous lung is less than that of normal healthy men, even at residual volume [29, 30]. Therefore, the higher volumes or percentages of LAA facilitate apnea-hypopnea formation in IPF due to the increase in collapsibility of upper airways.

Our results point out an easily available parameter for evaluating the OSA severity in IPF patients. It presents a new perspective for using radiologic findings in sleep medicine. These results also support the hypothesis of caudal retraction in the pathophysiology of apnea formation. Nevertheless, the small number of

patients and the lack of control group must be considered as the limitations of our study. Also, the effect of smoking must be highlighted in a larger scale study in which regression models with more variables can be established.

## CONCLUSION

Although LAA may include either emphysematous or hyperinflated areas, the positive correlation between AHI and LAA supports the hypothesis for the pathophysiology of OSA overlapping with restrictive lung diseases. Despite the small number of patients, the results of this study are informative for explaining the effect of LAA on the severity of OSAS in IPF patients. The caudal traction hypothesis can be based on the density of the lung considering the mixture of areas with different densities. The quantitative HRCT results which can be easily calculated via software can be used to predict the severity of OSAS in IPF patients. It is known that OSA had an impact on the quality of life for IPF patients. All IPF patients undergo HRCT. However, due to the limited number of sleep laboratories with busy schedules, PSG may be delayed. LAA which can be easily calculated from sections of CT scans can be used as a predictive factor for OSA in this population. The effect of LAA in the diagnosis and treatment of OSAS must be further investigated especially in patients who smoke or with underlying lung diseases.

*Authors' Contribution*

Study Conception: SŞD, HE, SF, DÇ; Study Design: SŞD, HE, SF, DÇ; Supervision: SŞD, HE, SF, DÇ; Funding: SŞD, HE, SF, DÇ; Materials: SŞD, HE, SF, DÇ; Data Collection and/or Processing: SŞD, HE, SF, DÇ; Statistical Analysis and/or Data Interpretation: SŞD, HE, SF, DÇ; Literature Review: SŞD, HE, SF, DÇ; Manuscript Preparation: SŞD, HE, SF, DÇ and Critical Review: SŞD, HE, SF, DÇ.

*Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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# Is there a difference between normotensive and hypertensive patients in terms of blood parameters and cardiovascular diseases?

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## ABSTRACT

**Objectives:** It has been stated in various studies that there is a difference in some blood parameters between hypertensive and normotensive patients for a long time. Mean platelet volume (MPV), and red blood cell distribution width (RDW), have been studied in hypertensive patient groups in many studies. Hypertension is a classic risk factor for ischemic stroke and myocardial ischemia, as known. In our study, we examined whether there was a difference between hypertensive patient groups and normotensive patients in terms of blood parameters such as MPV and RDW, and the incidence of stroke and myocardial infarction.

**Methods:** Blood samples and twenty-four-hour ambulatory blood pressure monitoring (ABPM) results of 552 patients admitted to our outpatient clinic with a pre-diagnosis of hypertension were retrospectively analyzed. According to ABPM results, we divided the study participants into four groups; dippers, non-dippers, extreme dippers, and normotansives. Complete blood count and biochemical test results were found in the database of our hospital for all patients and differences between groups were investigated.

**Results:** One hundred seventy three normotensives (Group 1) (mean age, 47.4 ± 15.4 years), 210 non-dippers (Group 2) (mean age, 53.8 ± 15.8 years), 67 extreme dippers (Group 3) (mean age, 49.1 ± 15.9 years) and 102 dippers (Group 4) (mean age, 52.2 ± 12.5 years). Daytime mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) and night-time mean SBP and DBP were significantly different in groups (Group 1: 117 [90-193] mmHg and 71 [55-87] mmHg; Group 2: 137 [107-188] mmHg and 83 [107-188] mmHg; Group 3: 143 [115-193] mmHg and 88 [56-122] mmHg; and Group 4: 140.5 [116-173] mmHg and 76 [55-124] mmHg), $p < 0.001$; respectively. MPV and RDW levels were different in all four groups ($p < 0.001$). We found a significant difference in the rates of stroke and coronary artery disease between the four groups ($p = 0.018$ and $p = 0.002$, respectively). In the ROC curve analysis MPV had sensitivity of %77. 8 and specificity of 78. 1% for stroke when the cut-off value MPV was 9.25 (Area under curve: 0.808, 95% confidence interval: 0.726-0.889, $p < 0.001$).

**Conclusions:** In our study, MPV and RDW levels and the rates of stroke and cardiovascular disease were significantly higher in non-dipper patients compared to other groups.

**Keywords:** Hypertension, platelet, inflammation, complications

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Arterial blood pressure has a circadian rhythm that affects cardiovascular outcomes [1]. In a normal population, average night-time systolic and diastolic blood pressure (BP) decrease %10-%20 compared to daytime BP. The dipping pattern is a 10% to 20% decrease in night-time mean systolic or diastolic BP relative to mean daytime BP. This drop rate is below 10% in the non-dipper group. The average night BP drop is over 20% in extreme dippers [2]. Previous studies demonstrated that as in the non-dipper group, the frequency of cardiovascular and cerebrovascular events increases in the extreme dipper group. Especially silent cerebral infarct rate increases in this group [3].

Red cell distribution width (RDW) increases due to increased erythrocyte destruction or ineffective erythropoiesis. Changes in the RDW interval may predict other cardiovascular disease outcomes [4, 5]. Previous studies demonstrated that hypertensive patients might have higher RDW levels according to patients with normal BP. In addition, in some studies, RDW levels were higher in the non-dipper group compared to the dipper group [6]. Mean platelet volume (MPV) is an indicator of platelet activation and platelet size, which is an independent risk factor for hypertension, myocardial infarction, and stroke [7, 8]. It is known that active large platelets containing denser granules are metabolically and enzymatically more active in triggering thrombosis than small ones [9].

In our study, we planned to compare MPV and RDW levels and the frequency of stroke and cardiovascular disease in between dippers, non-dippers, extreme-dippers, and normotensives.

## METHODS

### Study Population

The data and ambulatory blood pressure monitoring (ABPM) results of 552 patients over the age of 18 who were diagnosed with hypertension between January 2019 and June 2020 in our outpatient clinic were evaluated retrospectively. The patients were divided into four groups (dippers, non-dippers, normotensives, and extreme dippers) based on the results of ABPM. The exclusion criteria of this study were as follows; secondary hypertension, congestive heart failure, recent myocardial infarction (MI), peripheral vascular disease, valvular disease, having a history of metallic prosthetic valve surgery, angina pectoris, chronic renal failure (serum creatinine >1.5 mg/dl), chronic liver diseases, thromboembolic disorders, hematological disorders, acute or chronic infections. Patients under antiplatelet and warfarin treatment were also excluded from the study. Informed consent was obtained from all participants, and the study protocol was approved by the Namık Kemal University ethics committee.

### Ambulatory Blood Pressure Monitoring

Hypertension was defined as the mean of three different BP measurements above 140/90 mmHg. In ABPM average SBP > 135 mmHg, DBP > 85 mmHg at daytime (awake), average SBP >120 mmHg, DBP >70 mmHg at nighttime (asleep), or in average 24-hour measurements SBP >130 mmHg, DBP >80 mmHg defined as hypertension. Patients with a mean of three measurements below 140/90 in-office BP measurements and those with BP measurements below the above-mentioned values in ABPM were considered normotensive.

Blood pressure, heart rate was measured and recorded automatically by the ABPM system. (Darwin Professional Medilog; Schiller BR-102, Switzerland). The recorder was programmed to record at 30-minute intervals during the day (7:00 am-10:00 pm) and 1-hour intervals during the night (10:00 pm-7:00 am). Patients were subclassified according to the percentage difference between day and night systolic blood pressure (SBP) and diastolic blood pressure (DBP). Average nighttime SBP and DBP decrease %10-%20 compared to daytime BP. This group was named as dipper (Group 4). One hundred two patients who met this criterion were included in this group. The group with a decrease of 20% or more in systolic or diastolic BP at night compared to the daytime was named as extreme-dipper (Group 3). Sixty-seven patients were in the extreme dipper group. The group in which SBP or DBP at night decreased by 10 percent or less compared to daytime was named as non-dipper (Group 2). Two hundred ten patients were in this group. There were 173 normotensive patients as a control group (Group 1).

Baseline demographic data, current medications, and blood chemistry test results were collected from their medical records in our hospital. Blood samples were drawn from the antecubital vein between 08:00 am and 10:00 am after overnight fasting. EDTA

(dipotassium ethylendinitrotetraacetic acid) containing tubes were used for blood samples.

## Statistical Analysis

SPSS for Windows Version 22, 0 (SPSS Inc., IL, USA) was used for all statistical analysis. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as percentage. Whether the parameters conformed to the normal distribution was evaluated with the Kolmogorov Smirnov test. In statistical parameters such as RDW, MVP with normal distribution One-way ANOVA test was used for 4 groups. In post hoc analysis, parameters with equality of variance according to Levene's test were evaluated with Tukey's test, and parameters without equality of variance were evalu-

**Table 1. Baseline characteristics of the patient groups**

| Variables | GROUP 1 (n = 173) | GROUP 2 (n = 210) | GROUP 3 (n = 67) | GROUP 4 (n = 102) | Total (n = 552) | *p* value |
|---|---|---|---|---|---|---|
| Age (years) | 47.4 ± 15.4 | 53.8 ± 15.8 | 49.1 ± 15.9 | 52.2 ± 12.5 | 50.9 ± 15.3 | **< 0.001**[c] |
| Male, n (%) | 49 (28.3%) | 99 (47.1%) | 26 (38.8%) | 47 (46.1%) | 221 (40%) | **0.001**[a] |
| Female, n (%) | 124 (71.7%) | 111 (52.9%) | 41 (61.2%) | 55 (53.9%) | 331 (60%) | **0.001**[a] |
| CAD, n (%) | 12 (6.9%) | 34 (16.2%) | 2 (3%) | 16 (15.7%) | 64 (11.6%) | **0.002**[a] |
| Stroke, n (%) | 9 (5.2%) | 27 (12.9%) | 4 (6%) | 5 (4.9%) | 45 (8.2%) | **0.018**[a] |
| DM, n (%) | 28 (16.2%) | 48 (22.9%) | 12 (17.9%) | 23 (22.5%) | 111 (20.1%) | 0.358[a] |
| Glucose, mg/dl | 100 (75.6-176) | 101.65 (78.6-592) | 99 (76-264) | 102 (76-438) | 95.9 (75.6-592) | 0.060[b] |
| Hemoglobin, gr/dL | 13.19 ± 1.49 | 13.48 ± 1.73 | 13.3 ± 1.52 | 13.87 ± 1.56 | 13.47 ± 1.51 | 0.070[c] |
| Hematocrit, % | 40.1 ± 5.85 | 40 6 ± 4.84 | 41.04 ± 4.37 | 41.3 ± 4.52 | 40.76 ± 4.89 | 0.236[c] |
| Medical Treatment | | | | | | |
| Beta blocker, n (%) | 62 (35.8%) | 134 (63.8%) | 36 (53.7%) | 60 (58.8%) | 292 (52.9%) | **< 0.001**[a] |
| Ca–channel blocker, n (%) | 26 (15%) | 71 (33.8%) | 18 (27.5%) | 28 (27.5%) | 143 (25.9%) | **0.001**[a] |
| ACE-I/ARB, n (%) | 62 (35.8%) | 134 (63.8%) | 36 (53.7%) | 60 (58.8%) | 292 (52.9%) | **< 0.001**[a] |
| Diuretic, n (%) | 40 (23.1%) | 95 (45.2%) | 26 (38.8%) | 43 (42.2%) | 204 (37%) | **< 0.001**[a] |
| OAD, n (%) | 25 (14.5%) | 41 (19.5%) | 8 (11.9%) | 23 (22.5%) | 97 (17.6%) | 0.177[a] |
| Insulin, n (%) | 6 (3.5%) | 9 (4.3%) | 2 (3%) | 5 (4.9%) | 22 (4%) | 0.903[a] |
| Ambulatory blood pressure data | | | | | | |
| 24 hours mean SBP (mmHg) | 115 (90-132) | 137.5 (107-184) | 135 (111-189) | 136.5 (111-169) | 123 (90-189) | **< 0.001**[b] |
| 24 hour mean DBP (mmHg) | 69 (56-83) | 81.5 (61-122) | 81 (52-109) | 83 (56-105) | 74 (52-122) | **< 0.001**[b] |
| 24 hour mean HR beat/min | 73.9 ± 8.9 | 74.8 ± 9.9 | 74.2 ± 8.3 | 74.9 ± 9.2 | 74.5 ± 9.3 | 0.762[c] |
| Daytime mean SBP (mmHg) | 117 (90-193) | 137 (107-188) | 143 (115-193) | 140,5 (116-173) | 125 (90-193) | **< 0.001**[b] |
| Daytime mean DBP (mmHg) | 71 (55-87) | 83 (60-124) | 88 (56-122) | 87 (58-111) | 76 (55-124) | **< 0.001b** |
| Daytime mean HR beat/min | 76 (47-108) | 78 (50-111) | 77 (60-104) | 79 (55-98) | 73,5 (47-111) | 0.743[b] |
| Night-time mean SBP (mmHg) | 109.4 ± 8.6 | 139.5 ± 17 | 123.5 ± 16.4 | 129.8 ± 11.4 | 126.3 ± 18.7 | **< 0.001**[c] |
| Night-time mean DBP (mmHg) | 64 (49-78) | 80 (58-120) | 70 (45-90) | 76 (52-95) | 68 (45-120) | **<0.001**[b] |
| Night-time mean HR beat/min | 67 (37-95) | 70 (47-102) | 68 (53-91) | 68 (50-95) | 64 (37-102) | 0.132[b] |
| Daytime mean arterial pressure (mmHg) | 87 (48.67-101.67) | 100.33 (79.33-145.,33) | 105 (91.67-145.67) | 105.15 (84.7-131.7) | 93 (48.67-145.67) | **< 0.001**[b] |
| Night-time mean arterial pressure (mm Hg) | 79.09 ± 5.9 | 101.1 ± 11.9 | 87.5 ± 9.1 | 94.4 ± 7.5 | 91.3 ± 13.1 | **< 0.001**[c] |
| 24 hour mean arterial pressure (mmHg) | 83.6 (68.67-97) | 99 (82-142) | 97 (85.33-135.67) | 101.5 (80.7-126.3) | 90.67 (68.67-142) | **< 0.001**[b] |

BMI = Body mass index, SBP = Systolic blood pressure, DBP =Diastolic blood pressure, DM = Diabetes mellitus, HR = Heart rate, CAD = Coronary artery disease, OAD = Oral anti-diabetic. [a]Chi square test (percentage), [b]Kruskal Wallis (median [minimum-maximum]) [c]One Way Anova (mean ± standard deviation)

Group 1 = normotensives, Group 2 = non-dippers, Group 3 = extreme dippers, Group 4 = dippers

ated with Tamhane's test.Data that did not conform to normal distribution were compared using the Kruskal Wallis test.Mann-Whitney U test was used in subgroup analysis among 4 groups for parameters with significant differences. Frequency data were compared using the chi-square test. The cut-off value for MPV was calculated by performing roc analysis in individuals with strokes. *P*-value less than 0.05 was accepted statistically significant.

## RESULTS

The mean age of 552 patients was 50.9 ± 15.3 years and 221 (40%) were males, 331 (60%) were females. The patients were divided into 4 groups according to their 24-hour ambulatory BP measurements; Group 1: normotensives (mean age: 47.4 ± 15.4 years; 49 (28.3%) males, 124 (71.1%) females), Group 2 : non-dippers (mean age: 53.8 ± 15.8 years; 99 (47.1%) males, 111 (52.9%) females), Group 3: extreme dippers (mean age: 49.1 ± 15.9 years; 26 (38.8%) males, 41 (61.2%) females) and Group 4: dippers (mean age: 52.2 ± 12.5 years; 47 (46.1%) males, 55 (53.9%) females). The four groups were similar in terms of the number of diabetic patients ($p = 0.358$). There was no significant difference between the groups in terms of insulin and oral antidiabetic use ($p = 0.903$ and p = 0.177, respectively). Twenty-four-hours, daytime and night-time mean heart rates of patients were similar in the measurements of ambulatory BP ($p = 0.762$, $p = 0.743$ and $p = 0.132$, respectively). Their baseline characteristics were summarized in Table 1.

Subgroup analysis of patients characteristics between four groups were presented in Table 2. The mean age of the other three groups was higher than Group 1 ($p < 0.001$). Coronary artery disease rate was statistically similar in Group 3 and Group 4 ($p > 0.05$) but higher than normotensives ($p = 0.002$). The stroke rate was highest in Group 2, and it was observed at a statistically similar rate in the other groups ($p = 0.018$). Except for Group 1, the lipid levels of the patients in the three groups were similar. Compared with Group 1 in terms of total cholesterol, (TC) triglyceride and low-density lipoprotein cholestrerol (LDL-C) levels were higher in Group 2 ($p < 0.005$, $p < 0.001$ and p < 0.05 respectively). Triglyiceride levels in Group 3 and LDL-C levels in Group 4 were higher than Group 1. When we evaluated the biochemical parameters, the levels of MPW and RDW values were significantly higher in Group 2 ($p < 0.001$ for two values). These parameters were similar among other groups ($p > 0.05$). There was no difference between the groups in terms of other complete blood parameters and biochemical parameters.

The highest use of BP medication was in the non-dipper group ($p < 0.001$) and it was similar in Group 3 and Group 4 ($p > 0.05$). Daytime /Night-time mean DBP, Daytime/Night-time mean SBP, Day/Night-time mean arterial pressures were significantly different between groups. 24-hour mean SBP / DBP and 24-hour mean arterial pressure was similar in the 3 groups but higher than Group 1.

ROC curve analysis showed that MPV had a sensitivity of 77.8% and specificity of 78.1% for stroke in individuals who participated in the study when the cut- off value of MPV was 9.25 fl ($p < 0.001$) (Fig. 1).

## DISCUSSION

In our study, we found higher levels of MPV and RDW showing platelet activation in the non-dipper group compared to the other groups. Also, the frequency of cerebrovascular and coronary artery disease was higher in the non-dipper group.

In the long term, hypertension is a risk factor that should be controlled, causing end-organ damage and poor cardiovascular and cerebrovascular events [10]. Especially the non-dipper pattern is associated with target organ damage and poor cardiovascular outcomes in many studies [11]. In a meta-analysis in which prospective studies were examined, the dipping pattern and the mean night/day BP ratio significantly predicted mortality and cardiovascular events [12].

High MPV and RDW levels, which shown to be associated with inflammation and platelet activation, have been found to increase cardiovascular disease and mortality in hypertensive patients [13]. The underlying causes of high RDW levels are chronic inflammation, erythropoiesis disorders, increased erythrocyte destruction, and oxidative stress. RDW, a marker of inflammation, was found to be increased in non-dipper and dipper hypertensive patients compared to normotensive patients [14].

Ongoing oxidative stress and inflammation, in-

**Table 2. Subgroup analysis of patients characteristics between four groups**

| Variables | GROUP 1 (n = 173) | GROUP 2 (n = 210) | GROUP 3 (n = 67) | GROUP 4 (n = 102) | Total (n = 552) | *p* value |
|---|---|---|---|---|---|---|
| Age, (years)[3a] | 47.4 ± 15.4 | 53.8 ± 15.8 | 49 1 ± 15.9 | 52.2 ± 12.5 | 50.9 ± 15.3 | **< 0.001[a]** |
| MPV, fl[3a] | 8.52 ± 0.8 | 9.13 ± 1.05 | 8.74 ± 0.78 | 8.8 ± 0.79 | 8.83 ± 0.95 | **< 0.001[a,d,e]** |
| RDW, %[3a] | 13.1 ± 1.4 | 13.8 ± 1.39 | 13.3 ± 1.27 | 13.01 ± 1.2 | 13.42 ± 1.38 | **< 0.001[a,d,e]** |
| Hemoglobin, g/dL[3a] | 13.19 ± 1.49 | 13.48 ± 1.73 | 13.3 ± 1.52 | 13.87 ± 1.56 | 13.47 ± 1.51 | **0.008[c]** |
| Platelet ($10^3/\mu L$)[2] | 254 (131-448) | 242 (72-542) | 198 (155.2-330) | 197.15 (98.2-352) | 229 (72-547) | **0.024** |
| Creatinine(mg/dL)[2] | 0.72 (0.36-0.9) | 0.78 (0.43-3.89) | 0.73 (0.34-1.85) | 0.76 (0.49-1.68) | 0.69 (0.34-6.89) | **0.005[a]** |
| Total Cholesterol (mg/dL)[2] | 185 (59.5-354.4) | 201.4 (98.9-357) | 198 (155.2-330) | 197.15 (98.2-352) | 179.5 (59.5-357) | **0.003[a,b,c]** |
| LDL-C (mg/dL)[2] | 106.78 (19.8-254.32) | 120 (35-232.7) | 120 (68-220) | 117.71 (31.96-256) | 101.16 (19.8-256) | **0.009[a,b]** |
| HDL-C (mg/dL)[2] | 48 (21-125) | 45 (20-97) | 48 (32-84) | 49 (30-106) | 41(20-125) | **0.015a,d,e** |
| Triglyceride (mg/dL)[2] | 117.3 (35.6-1119) | 149.75 (47-650) | 136 (50-478) | 120.4 (45.7-526.2) | 105 (35.6-1119) | **< 0.001[a]** |
| CAD, n (%)[1] | 8 (4.62%)[x] | 34 (16.2%)[y] | 5 (7.46%)[z] | 7 (6.8%)[z] | 54 (9.7%) | **0.002** |
| Stroke, n (%)[1] | 9 (5.2%)[x] | 27 (12.9%)[y] | 4 (6%)[x] | 5 (4.9%)[x] | 45 (8.2%) | **0.018** |
| Gender[1] | | | | | | |
| Male, n (%)[1] | 49 (28.3%)[x] | 99 (47.1%)[y] | 26 (38.8%)[z] | 47 (46.1%)[y] | 221 (40%) | **0.001** |
| Female, n (%)[1] | 124 (71.7%)[x] | 111 (52.9%)[y] | 41 (61.2%)[z] | 55 (53.9%)[y] | 331 (60%) | **0.001** |
| Beta blocker, n (%)[1] | 62 (35.8%)[x] | 134 (63.8%)[y] | 36 (53.7%)[z] | 60 (58.8%)[z] | 292 (52.9%) | **< 0.001** |
| Ca –channel blocker, n (%)[1] | 26 (15%)[x] | 71 (33.8%)[y] | 18(26.9%)[z] | 28 (27.5%)[z] | 143 (25.9%) | **0.001** |
| ACE I/ARB, n (%)[1] | 62 (35.8%)[x] | 134 (63.8%)[y] | 36 (53.7%)[z] | 60 (58.8%)[y] | 292 (52.9%) | **< 0.001** |
| Diuretic, n (%)[1] | 40 (23.1%)[x] | 95 (45.2%)[y] | 26 (38.8%)[z] | 43 (42.2%)[y] | 204 (37%) | **< 0.001** |
| 24 hours mean SBP (mmHg)[2] | 115 (90-132) | 137.5 (107-184) | 135 (111-189) | 136,5 (111-169) | 123 (90-189) | **< 0.001[a,b,c]** |
| 24 hours mean DBP (mmHg)[2] | 69 (56-83) | 81.5 (61-122) | 81 (52-109) | 83 (56-105) | 74 (52-122) | **< 0.001[a,b,c]** |
| Daytime mean SBP (mmHg)[2] | 117 (90-193) | 137 (107-188) | 143 (115-193) | 140,5 (116-173) | 125 (90-193) | **< 0.001[a,b,c,d,e,f]** |
| Daytime mean DBP (mmHg)[2] | 71 (55-87) | 83 (60-124) | 88 (56-122) | 87 (58-111) | 76 (55-124) | **< 0.001[a,b,c,d,e,f]** |
| Night-time mean SBP (mmHg)[3b] | 109.4 ± 8.6 | 139.5 ± 17 | 123.5 ± 16.4 | 129.8 ± 11.4 | 126.3 ± 18.7 | **< 0,001[a,b,c,d,e,f]** |
| Night-time mean DBP (mmHg)[2] | 64 (49-78) | 80 (58-120) | 70 (45-90) | 76 (52-95) | 68 (45-120) | **< 0.001[a,b,c,d,e,f]** |
| Daytime mean arterial pressure (mmHg)[2] | 87 (48.67-101.67) | 100.33 (79.33-145.33) | 105 (91.67-145.67) | 105.15 (84.7-131.7) | 93 (48.67-145.67) | **< 0.001[a,b,c,d,e,f]** |
| Night-time mean arterial pressure (mmHg)[3b] | 79.09 ± 5.9 | 101.1 ± 11.9 | 87.5 ± 9.1 | 94.4 ± 7.5 | 91.3 ± 13.1 | **< 0.001[a,b,c,d,e,f]** |
| 24 hour mean arterial pressure (mmHg)[2] | 83.6 (68.67-97) | 99 (82-142) | 97 (85.33-135.67) | 101.5 (80.7-126.3) | 90.67 (68.67-142) | **< 0.001[a,b,c]** |

MPV = Mean platelet volume, RDW = Red cell distribution width, LDL-C = Low density lipoprotein cholesterol, HDL-C = High density lipoprotein cholesterol, CAD = Coronary artery disease, ACEI = Angiotensin converting enzyme inhibitor ARB = Angiotensin receptor blocker, SBP = Systolic blood pressure, DBP = Diastolic blood pressure. Group 1 = normotensives, Group 2 = non-dippers, Group 3 = extreme dippers, Group 4 = dippers

[a]$p < 0.05$ in subgroup analysis compare to Group 1and Group 2, [b]$p < 0.05$ in subgroup analysis compare to Group 1 and Group 3, [c]:$p < 0.05$ in subgroup analysis compare to Group1 and Group 4, [d] $p < 0.05$ in subgroup analysis compare to Group 2 and Group 3, [e]:$p < 0.05$ in subgroup analysis compare to Group 2 and Group 4, [f]: $p < 0.05$ in subgroup analysis compare to Group 3 and Group 4.

Each subscript letter ((shown as (x, y, z)) denotes a subset of grup categories whose column proportions do not differ significantly from each other at the 0.05 level in Chi square subgroup analysis. Bonferroni correction was made in subgroup analysis of parameters with kruskal wallis test. $p$ value < 0.008 was considered significant. [1]Chi square test(percentage), [2]Kruskal Wallis (median (minimum-maximum)), [3]One Way Anova (mean ± standard deviation). [3a]; post hoc analysis with Tukey test, [3b]; post hoc analysis with Tamhane test

creased cytokine levels, especially in atherosclerosis and hypertension may have caused an increase in RDW levels by suppressing erythrocyte production in the bone marrow. Also increased sympathetic activity and angiotensin II levels, especially in non-dipper patients can stimulate the proliferation of erythrocyte progenitors and increase the RDW range [15]. In our study, we found higher RDW levels in non-dipper patients compared to the control group and the other two groups.

Mean platelet volume is the quantitative indicator of mean platelet size. Platelets are small, seedless,

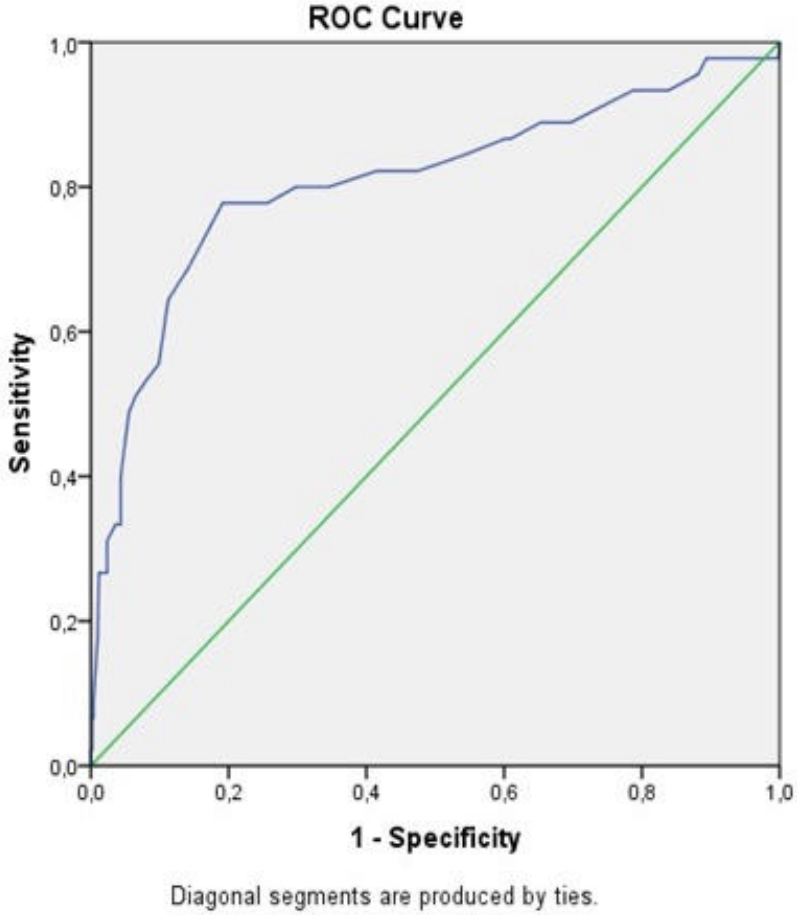


**Fig. 1. ROC (Receiver operation characteristic) curve and AUC (Area under the curve) for mean platelet volume for predicting stroke in hypertensive patients (Cut off: 9.25, AUC: 0.808, 95% CI:0,726- 0.889, p < 0.001, 77.8% sensitivity and 78.1% specificity).**

round-shaped specialized blood cells 2-4 μm in diameter. Large platelets are metabolically and enzymatically more active than small ones, which increases the susceptibility to thrombosis. As the MPV increases, the expression of glycoprotein Ib and glycoprotein IIb/IIIa receptors on its surface increases. Large platelets have denser granules where more proagretory factors [16, 17]. In our study, we found higher MPV levels in non-dipper patients compared to the control group and the other two groups. Stroke and coronary artery disease rates were again higher in the non-dipper group.

In studies conducted with healthy volunteers, platelet aggregation has been shown to increase in the morning hours of the day [18]. This situation increases the risk of acute myocardial infarction in non-dipper patients with increased MPV levels. An increase in BP has been closely associated with mortality in ischemic events. Moreover, every 20 mmHg increase in SBP and every 10 mmHg increase in DBP increase the mortality rate two-fold indicated that the development of atherosclerotic plaque increased in non-dipper hypertensive patients and high BP at night caused endothelial damage [19].

In various studies, extreme dipper and dipper hypertensives were found to be similar in terms of cardiovascular prognosis [20]. However, different studies are documenting a better or worse prognosis in extreme dipper patients. The extreme dipper pattern ranges from 5% to 30% depending on the diagnostic criteria, clinical and demographic characteristics of the individuals [20]. In a study by Ohkubo *et al*. [21], the mortality risk was highest in reverse dippers, followed by non dippers; the lowest risk was associated with extreme dipping and dipper patients. In subgroup analysis, there was no difference between dipper and extreme dipper groups [21]. Additionally, a meta-analysis of several studies providing data on echocardiographic left ventricular hypertrophy indicates that extreme dippers have a lower risk of subclinical car-

diac injury than dippers and reverse dippers [22]. Evidence of the relationship between symptomatic or silent cerebral ischemic lesions assessed by imaging techniques and nocturnal BP reduction is limited to a few studies in elderly hypertensive patients [22]. Severe nighttime BP reduction leading to cerebral hypoperfusion possibly related to antihypertensive therapy. However, the presence of an extreme dipper pattern, potentially harmful to cerebral perfusion, should be excluded in treated elderly hypertensive patients (especially if taking antihypertensive drugs in the afternoon or evening). However, data from the large database suggest that extreme dippers tend to be younger, less frequently obese, diabetic, or affected by cardiovascular disease. In our study, stroke rates were the highest in the non-dipper group [22]. In our study, it was similar in the extreme dipper, dipper, and normotensive groups. Coronary artery disease rates were highest in the non-dipper group. This ratio was similar in extreme dipper and dipper groups.

### Limitations

The fact that our study was planned in a single center and the low number of patients participating in the study limits the power of our findings. In addition, in our study, we did not include patients with advanced heart failure, secondary hypertension, new heart attack, or valvular heart disease. Therefore, the results of our study cannot be attributed to all hypertensive patient groups.

## CONCLUSION

In our study, we found higher levels of MPV and RDW showing platelet activation in the non-dipper group compared to the other groups. Also, the frequency of cerebrovascular and coronary artery disease was higher in the non-dipper group. In addition, as mentioned in some studies, we found the frequency of cerebrovascular and coronary artery disease, which is claimed to be more common in extreme dipper patients, to be similar to the dipper group.

*Authors' Contribution*

Study Conception: CA, ŞA; Study Design: CA, ŞA; Supervision: CA, ŞA, ME, ŞY; Funding: CA, ŞA; Materials: CA, ŞA; Data Collection and/or Processing: CA, ŞA; Statistical Analysis and/or Data Interpretation: CA, ŞA, ME, ŞY; Literature Review: CA, ŞA, ME, ŞY; CA, ŞA, ME, ŞY: AAP and Critical Review: CA, ŞA, ME, ŞY.

*Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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# Prevalence of aspirin and clopidogrel resistance in neurovascular stenting: a single-center experience

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## ABSTRACT

**Objectives:** The objective of this study was to determine the frequency of aspirin and clopidogrel resistance of patients undergoing neurovascular stenting procedure in the interventional radiology unit.

**Methods:** The Multiplate® Analyzer (Roche Diagnostics, Germany) test data of 250 patients who underwent carotid or intracranial artery stenting due to atherosclerotic stenosis or treatment of intracranial aneurysms between 2013-2017 in the Interventional Radiology Unit of our hospital were evaluated retrospectively to detect the aspirin and clopidogrel resistance. Aspirin or clopidogrel resistance defined as the higher AUC value than 40U and 46U, respectively. The patients who did not have a result of the Multiplate® test; had anemia, known coagulation disorder or thrombocytopenia were excluded.

**Results:** Among the 172 patients who met the inclusion criteria, 59 (34.3%) were those who had an intracranial stent during aneurysm treatment, and 113 (65.7%) had carotid stenting due to atherosclerotic stenosis. The prevalence of aspirin resistance was 9.4% (16/170) whereas that of clopidogrel resistance was 23.8% (41/172). Among the patients with atherosclerotic stenosis, aspirin resistance accounting for 3.6%, and clopidogrel resistance was 23.0%. Furthermore, the resistance in the patients with stent-assisted coiling for aneurysm treatment was 20.7% for aspirin and 25.4% for clopidogrel.

**Conclusions:** In our study, the prevalence of aspirin resistance was found 9.4% and clopidogrel resistance 23.8% in patients who had neurovascular stenting. The effect of this condition on clinical outcomes in these patients should be investigated by randomized controlled trials.

**Keywords:** Neurovascular stenting, aspirin resistance, clopidogrel resistance, multiplate test, antiplatelet resistance

Dual antiplatelet treatment with aspirin (acetylsalicylic acid) and clopidogrel has been readily accepted regiment of antithrombotic therapy in patients undergoing neurovascular stenting [1]. Although these antithrombotics have been used in patients as premedication and after neurovascular stenting procedure, thromboembolic complications have still been encountered during or/and after the procedure [2].

Insufficient in vivo platelet inhibition with aspirin and clopidogrel have been accused of thromboembolic complications theoretically. If inadequate platelet inhibition is demonstrated with a laboratory test, the terms 'resistance to aspirin or clopidogrel', 'low response to aspirin-clopidogrel', or 'nonresponse to aspirin-clopidogrel' have been used. In vitro laboratory tests detecting platelet function, namely Multiplate®,

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VerifyNow®, Light Transmission Aggregometry (LTA), PFA-100 (Platelet Function Assay), VASP (vasodilator-stimulated phosphoprotein), have been used excessively among patients with cardiovascular intervention in order to indicate patients with inadequate platelet inhibition [3]. This trend has been adopted in the field of neurovascular intervention by some centres and the Multiplate® test has been used in our neurovascular interventional unit for this purpose.

Providing antiplatelet drug resistance could be determined before neurovascular stenting, antiplatelet dosage and combination might be adjusted on an individual basis to prevent new thromboembolic events [4]. Therefore, it might be important to know the inadequate response to aspirin and clopidogrel in patients who will have neurovascular stent-placement procedures. In this study, we aimed to detect the frequency of aspirin and clopidogrel resistance in patients undergoing neurovascular stenting in the interventional radiology unit of our hospital.

## METHODS

### Patient Group

Patients who underwent elective intracranial or extracranial stent placement with different indications at the Interventional Radiology Unit of our (the name hidden for blinded review) University, Faculty of Medicine, Department of Radiology between January 1, 2013 and January 31, 2017 were assessed.

The patients who did not receive aspirin or clopidogrel for any reason or did not have a complete result of the resistance test; had anemia (Hg level < 8 g/dl), known coagulation disorder or thrombocytopenia (< 50.000 /$m^3$), polycythemia, leukopenia (leukocytes < 4.000 /mm), bone marrow disease or blood transfusion were excluded. In addition, those whom taken blood samples could not be processed between 30 minutes and 3 hours were not included.

Records of patients in the study were retrospectively reviewed and the data were collected including age, sex, and presence of concomitant diseases such as hypertension, diabetes, cerebrovascular event (CVO), coronary artery disease (CAD), hypercholesterolemia, chronic kidney disease (CKD) and chronic liver disease. Moreover, results of the fasting blood samples obtained on the day before or on the day of the procedure were evaluated to note blood glucose, creatinine, hemoglobin, platelet, and leukocyte counts.

Routine screening for clinically silent ischemic strokes with diffusion-weighted imaging was not performed. Post-procedural images of patients (unenhanced computed tomography or magnetic resonance imaging) were retrospectively examined for possible new ischemic findings by comparison with pre-procedural imaging.

### Medication of Patients

Patients scheduled for elective neurovascular stent placement received 100 mg aspirin and 75 mg clopidogrel per day for 7 days prior to the procedure normally. If there were less than 7 days to the procedure, 300 mg clopidogrel and aspirin per day were given for 3 days and then continued with 100 mg aspirin and 75 mg clopidogrel daily. None of our patients received 600 mg clopidogrel as a loading dose just before the day of the procedure.

If the clopidogrel resistance was demonstrated by Multiplate® test, the premedication was adjusted as 500 mg of ticlopidine and 100 mg of aspirin for 7 days before the procedure. In case of still antiplatelet resistance presence, prasugrel 10 mg per day alone was given 7 days before the procedure.

### Multiplate® test

Venous blood samples were collected 24 hours before the procedure from the peripheral antecubital vein by nurses. Blood samples were filled into hirudin filled tubes after which they were sent to the hematology laboratory within 30 minutes. Platelet function tests were studied with the Multiplate® analysis system (Fig. 1). Blood samples were stored at room temperature for 30 minutes. Platelet aggregation was evaluated using the impedance method within 30-180 minutes in total after samples were collected. 300 microliters of the blood sample were taken and were diluted again with 300 microliters of 0.9% saline at room temperature. 20 microliters ADP or ASP test agents were added into these sample after 3 minutes incubation period.

The results were obtained by calculating the area under the curve (AUC) at the end of the 6 minute evaluation period. The recommended range for AUC values is 71-115U for aspirin and 57-113U for clopidogrel. Aspirin Multiplate® test results above 40U

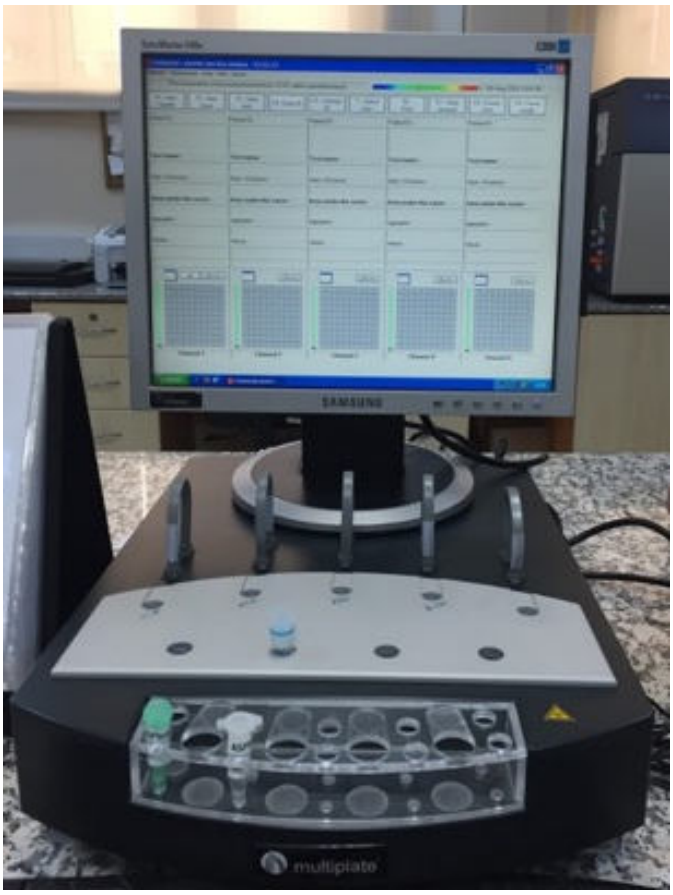


**Fig. 1. Multiplate Test Machine. Multiplate test machine in our hospital is located in Hematology laboratary; however, it is possible to be situated and utilized it with a trained staff in interventional radiology units.**

were recorded as the group showing aspirin resistance while for clopidogrel, those with a result above 46U were recorded as with clopidogrel resistance. Follow-up platelet-activity testing was not performed after the procedure.

### Statistical Analysis

SSPS version 23.0 was used for statistical analysis. The patients were divided into two groups as stenting due to atherosclerotic stenosis and stent-assisted coil embolization for aneurysm treatment. For these two groups, separately, and all patients are searched for aspirin and clopidogrel resistance. The two groups were compared in terms of the frequency of resistance. Clinical characteristics were also compared between these two groups, as well as the resistant versus non-resistant groups. The independent samples t-test, Mann Whitney U test, and Chi square tests were used to determine the correlations between the variables. A $p$ value of $< 0.05$ was considered statistically significant. The study was approved by the ethics committee of our hospital.

## RESULTS

In this study, 250 patients who underwent neurovascular stenting in the Interventional Radiology Unit of our hospital between 2013 and 2017 were identified. 78 of these were excluded since 74 of them those whom could not be reached the complete Multiplate® test results, 2 of them had severe anemia and the remaining 2 had severe thrombocytopenia. 57 (33.1%) of the patients were female while 115 (66.9%) were male. The mean age was 65.6 (20-92) years. Of the remaining 172 patients, 59 (34.3%) were those the intracranial stents were implanted during aneurysm embolization, and 113 (65.7%) were the ones who had stenting for the treatment of atherosclerotic stenosis. Flow diverter devices were used in 35 (20.3%) patients who had stent placement during aneurysm treatment. The prevalance of aspirin resistance was 9.4% (16/170) in all patients whereas that of clopidogrel was 23.8% (41/172). There were 9 (5%) patients with both aspirin and clopidogrel resistance.

When the group with aspirin resistance was compared with the group without resistance, a significant difference was found between the ages ($p = 0.005$). The mean age was 57.4 ± 12.2 years in the resistant group while it was 66.6 ± 12.8 years in the nonresistant group. There were no significant difference between resistant and non-resistant groups in terms of concomitant diseases; diabetes, hypertension, coronary artery disease, and dyslipidemia. Moreover, no significant difference was found between the two groups concerning thromboembolic findings in the cranial MR or CT (Table 1).

When the group with clopidogrel resistance and the one without resistance were compared; the presence of diabetes was found 63.4% in the resistant group, while it was 26.0% in the non-resistant group ($p < 0.001$). There was no significant difference between the two groups in other parameters (Table 2).

Aspirin resistance was 3.6% and clopidogrel resistance was 23.0% in the stent-implanted group due to atherosclerotic stenosis, whereas the resistance in the stent-assisted aneurysm treatment group was

**Table 1. Comparison between the group with aspirin resistance and without resistance**

| Parameter | Group with Aspirin resistance (n = 16) | Group without Aspirin resistance (n = 154) | *p* value |
|---|---|---|---|
| Age (years) | 57.38 ± 12.2 | 66.61 ± 12.8 | **0.005** |
| Gender (female) | 43.8% | 31.2% | 0.457 |
| Diabetus mellitus | 37.5% | 33.8% | 0.982 |
| Hypertension | 56.3% | 63.0% | 0.796 |
| Coronary arterial disease | 25.0% | 26.0% | 1.000 |
| Dyslipidaemia | 18.8% | 38.3% | 0.203 |
| Chronic kidney disease | 0.0% | 3.2% | 1.000 |
| Radiologic thromboembolic findings | 20.0% | 32.2% | 0.720 |
| Creatinine (mg/dl) | 0.77 ± 0.2 | 0.89 ± 0.25 | 0.026 |
| Glucose (mg/dl) | 144.9 ± 65.2 | 132.5 ± 91.7 | 0.187 |
| Leukocyte ($\times 10^9$) | 8.4 ± 3.2 | 8.6 ± 3.2 | 0.839 |
| Platelet ($\times 10^9$) | 225.6 ± 72.8 | 229.2 ± 71.1 | 0.892 |
| Hemoglobin (g/dl) | 12.8 ± 1.3 | 12.9 ± 1.6 | 0.764 |

Data are shown as mean ± standard deviation or n (%)

**Table 2. Comparison between the group with clopidogrel resistance and without resistance**

| Parameter | Group with Clopidogrel resistance (n = 41) | Group without Clopidogrel resistance (n = 131) | *p* value |
|---|---|---|---|
| Age (years | 65.9 ± 11.4 | 65.60 ± 13.4 | 0.960 |
| Gender (female) | 36.6% | 32.1% | 0.729 |
| Diabetus mellitus | 63.4% | 26.0% | **< 0.001** |
| Hypertension | 68.3% | 61.1% | 0.516 |
| Coronary arterial disease | 25.0% | 26.0% | 0.259 |
| Dyslipidaemia | 41.5% | 34.4% | 0.521 |
| Chronic kidney disease | 4.9% | 2.3% | 0.594 |
| Radiologic thromboembolic findings | 20.0% | 34.7% | 0.261 |
| Creatinine (mg/dl) | 0.88 ± 0.28 | 0.88 ± 0.24 | 0.934 |
| Glucose (mg/dl) | 128.4 ± 51.4 | 135.5 ± 97.9 | 0.994 |
| Leukocyte ($\times 10^9$) | 8.5 ± 3 | 8.5 ± 3.2 | 0.872 |
| Platelet ($\times 10^9$) | 238 ± 53.6 | 225 ± 75.6 | 0.118 |
| Hemoglobin (g/dl) | 12.6 ± 1.5 | 12.9 ± 1.5 | 0.237 |

Data are shown as mean ± standard deviation or n (%)

**Table 3. The Aspirin and Clopidogrel resistance literature among patients with neurovascular procedures**

| Author and year | Number of patients | Procedure | Antiplatelet treatment | Antiplatelet Resistance test | Test Cut-off value | Prevalence of Aspirin Resistance | Prevalence of Clopidogrel Resistance |
|---|---|---|---|---|---|---|---|
| Lee *et al.* 2008 | 98 | Stent placement (Intracranial aneurysm treatment or intra-extracranial artery stenosis) | Clp 300 mg loading dose followed by 75 mg Clp daily +325 mg Asp (5-10 days before) | VerifyNow | ARU ≥550, P2Y12 % İnhibition ≤40% | 2.1% | 42.9% |
| Müller-Schunk *et al.* 2008 | 50 | Stent placement (intra-extracranial artery stenosis) | Asp 100 mg+ 300 mg Clp loading dose 12 hours before procedure or if there were more than 48 hours to procedure75 mg Clp daily | Multiplate | >52 ARU | | 28% |
| Prabhakaran *et al.* 2008 | 76 | Stent placement (Intracranial aneurysm treatment or intra-extracranial artery stenosis) | Only Asp, Only Clp or Asp + Clp (1week before procedure) | VerifyNow | ARU ≥550, P2Y12 % İnhibition ≤40% | 4.2% | 50.9% |
| Reavey-Cantwell *et al.* 2009 | 81 | Aneurysm embolization with or without stent placement or stent placement for intra-extracranial artery stenosis | Asp 325 mg + Clp 75 mg daily (7 days before) | PFA-100 | PFA1 >209 or if PFA1 between 189-210 PFA2 >126 | 21% | |
| Dal-Sung Ryu *et al.* 2010 | 53 | Coil embolization of aneurysm or intracranial stent placement or both | 100 mg Asp + 75 mg Clp daily (at least 3 days before) | VerifyNow | ARU≥550 P2Y12 % inhibition≤40% | 17% | 62.3% |
| Pandya *et al.* 2010 | 216 | Aneurysm embolization and stent placement (Intracranial aneurysm treatment or intra-extracranial artery stenosis) | Asp 81 mg + Clp 75 mg daily (if there is 7 days before procedure) or Clp 300-600 mg + Asp 325 mg loading dose (just before the procedure) | VerifyNow | ARU≥550 P2Y12 % inhibition≤50% | 12% | 34% |
| Drazin *et al.* 2011 | 52 | Stent placement (Intracranial aneurysm treatment or intra-extracranial artery stenosis) | 81 mg Aspirin+600 mg Clp (12 hours before the procedure) followed by 75 mg Clp + 81 mg Asp daily (if resistance shown 300 mg or 600 mg loading dose of Clp) | VerifyNow | ARU >550, P2Y12 % İnhibition <20% | 13.5% | 36.5% |
| Koerner *et al.* 2012 | 44 | Stent placement (intra-extracranial artery percutan transluminal angioplasty) | Asp 100 mg + Clp 75 mg (at least 3 days before) or Clp 300 mg + Asp 500 mg loading dose (just before the procedure) | Multiplate | > 468 ARU | | 25% |
| Delgado Almandoz *et al.* 2013 | 44 | Aneurysm treatment with Pipeline stent placement | Asp 325 mg+ Clp 75 mg daily | VerifyNow | PRU >200 | | 26.2% |
| Fifi *et al.* 2013 | 96 | Stent placement (Intracranial aneurysm treatment or intra-extracranial artery stenosis) | Asp 81 mg +75 mg Clp daily (5 days before) or 600 mg Clp loading dose in emergency cases) | VerifyNow | ARU ≥ 550 P2Y12 % inhibition ≤20% | 5.2% | 36.5% |
| Heller *et al.* 2013 | 25 | Aneurysm treatment with Pipeline stent placement | Asp (325 or 81 mg) and Clp 75 mg daily (7 days before) | LTA | ASA maximum platelet aggregation >20%, CLP MPA >60% | 16% | 4% |
| Nordeen *et al.* 2013 | 81 | Stent placement (Intracranial aneurysm treatment or intra-extracranial artery stenosis) | Asp 325 mg +75 mg Clp daily (5-7 days before) (600 mg Clp and 650 mg Asp loading dose in emergency cases) | VerifyNow | P2Y12 % inhibition <20% | | 21% |
| Kashiwazaki *et al.* 2014 | 66 | Stent placement (Intracranial aneurysm treatment or intra-extracranial artery stenosis) | Asp 100 mg+ Clp 75 mg daily (14 days before) or Clp 300 mg+ Asp 500 mg loading dose(just before the procedure) | VerifyNow | P2Y12 % inhibition ≤26% | | 28.8% |
| Oran *et al.* 2015 | 68 | Aneurysm treatment with flow diverter devices | Asp 300 mg+ Clp 600 mg loading dose (8-12 hours before) | Multiplate | Asp AUC >500, CLP AUC >468 | | 25% |
| Hwang *et al.* 2015 | 228 | The treatment of unruptured aneurysm with coil embolization | Asp 100 mg +75 mg Clp daily (5 days before) If resistance shown Asp 300 mg+ 200 mg cilastazol | VerifyNow | ARU ≥550 PRU ≥213 | Resistance in general 55.3% | Resistance in general 55.3% |
| Tan et al. 2015 | 74 | Aneurysm treatment with Pipeline stent placement | Asp 325 mg +75 mg Clp daily (5 day before) or Clp 600 mg, Asp 325 mg loading dose (2 hours before) | VerifyNow | PRU >208 | | 52.7% |
| Wong *et al.* 2015 | 32 | Stent placement (Intracranial aneurysm treatment or intra-extracranial artery stenosis) | Asp 325 mg +75 mg Clp daily (7 days before) | VerifyNow | PRU 120-180 normal | | 53.1% |
| Flechtenmacher *et al.* 2015 | 97 | Stent placement (Intracranial aneurysm treatment or intra-extracranial artery stenosis) | Asp 100 mg +75 mg Clp daily (5 days before) or Clp 600 mg loading dose (1 day before) | LTA<br>VerifyNow<br>Multiplate | >40%<br>PRU>236<br>ARU>40 U | | 47.6%<br>50.5%<br>35.9% |
| Asai *et al.* 2015 | 189 | Aneurysm embolization with or without stent placement | Asp and Clp daily (5-7 days before) | VerifyNow | PRU ≥ 230 | 5.8% | 34.9% |
| Kim *et al.* 2016 | 338 | The treatment of unruptured aneurysms with coil embolization (with or without stent placement) | Asp 100 mg +75 mg Clp daily (7 days before) | VerifyNow | ARU ≥550 PRU ≥240 | 9.5% | 31.1% |
| Song *et al.* 2017 | 99 | The treatment of unruptured aneurysms with stent-assisted coil embolization | 100 mg asp+75 mg Clp daily (5-7 days before) or 300mg asp+ 600 mg Clp loading dose (on the procedure day) | VerifyNow | ARU≥550 PRU≥240 | 12% | 62.6% |
| Adeeb *et al.* 2017 | 402 | Aneurysm treatment with Pipeline stent placement | 325 mg asp+ 75 mg Clp daily (3-14 days before) | LTA<br>VerifyNow<br>Whole-blood lumiaggregometry | ASA platelet aggregation >20%,<br>PRU>208<br>>6 Ω | | 28.8% |

Clp = clopidogrel, Asp = Aspirin, ARU = aspirin reaction unit, PRU = P2Y12 reaction unit, LTA = Light Transmission Aggregometry, AUC = area under curve, ASA= acetylsalicylic acid, PFA-100 = Platelet Function Assay

20.7% and 25.4%, respectively. Aspirin resistance was significantly higher in the latter group compared to the former ($p < 0.001$). However, there was no difference between these two groups in terms of clopidogrel resistance. The resistance frequency in the patients who had flow diverter device was 17.6% for aspirin and 25.7% for clopidogrel.

## DISCUSSION

In patients undergoing cerebrovascular stenting, development of thromboembolic complications due to platelet aggregation induced by usage of endovascular devices is the main problem [2]. Dual antiplatelet therapy with asprin and clopidogrel has been accepted as premedication method and post-procedural treatment in order to prevent these complications. However, the use of platelet function tests before neurosurgical procedures remains controversial. In contrast to lack of literature in neuravascular patients, the frequency of aspirin and clopidogrel resistance has been shown in different groups of patients receiving dual antiplatelet therapy (percutaneous coronary intervention, peripheral arterial disease, ischemic stroke, diabetes mellitus, etc.) and its effect on clinical outcomes is discussed [3, 5-10].

Several studies in the cardiology literature have shown that the incidence of aspirin resistance varies according to how it is defined and the differences in dosage and population used. The prevalence of aspirin resistance in patients undergoing percutaneous coronary intervention has been in a wide range of 1-55% [5]. In addition, clopidogrel resistance has been reported up to 35% in that patient group so far [3]. However, a number of multicenter, randomized controlled trials (GRAVITAS, ARCTIC, TRIGGER-PC), which were subsequently performed in patients with percutaneous coronary interventional procedures, did not show the overall clinical benefit of antiplatelet therapy according to the results of platelet function tests [6-8].

In studies conducted into patients with peripheral arterial disease, the incidence of aspirin resistance has been reported up to 60% and clopidogrel resistance up to 65% [9]. In several studies on ischemic stroke patients, aspirin and clopidogrel resistance rate was found to be 23% and 27%, respectively. Moreover, the risk of recurrent ischemic stroke or transient ischemic attack was reported higher in those patients with resistance to antiplatelets [10].

In patients undergoing neurovascular interventional procedures, platelet resistance tests, frequency of resistance and their association with clinical outcomes have been investigated in retrospective, single-center studies. In our study, the frequency of resistance was found to be 9.4% for aspirin and 23.8% for clopidogrel by Multiplate® test and they were similar to the frequency rates found in in the studies conducted so far. In these studies the prevelance of aspirin resistance was found to be between 2.1-17% and the frequency of clopidogrel resistance was found between 21-62.6% (Table 3) [2, 4, 11-28].

The patients with flow diverter stents evaluated seperately given the being more excessively used in last ten years and the frequency of resistance was found to be 17.6% for aspirin and 25.7% for clopidogrel in 35 patients with flow diverter devices at our hospital. Delgado Almandoz *et al*. [14] and Heller *et al*. [23] found the low response rate of clopidogrel in patients who underwent aneurysm treatment with flow diverter devices 26.2% (n = 44) and 4 % (n = 24), respectively. Oran *et al*. [4] revealed the low response rate of clopidogrel to be 25% (n = 100) with Multiplate® test in a group of patients with FDD and this rate is similar to ours. Moreover, Tan *et al*. [24] found the frequency of low response to clopidogrel to be 52.7% (n = 74) using FDD by VerifyNow test, which is the highest frequency of resistance reported to clopidogrel among patients with FDD.

The premedications with new antiplatelets, such as prasugrel and ticagrelor, are becoming increasingly used in neurovascular stenting, particularly with FDDs. In our unit, we prefer ticlopidine and prasugrel as premedication in patients who are resistant to clopidogrel. In a systematic review, dual antiplatelet regimens including ticagrelor or prasugrel are found to be safe for patients undergoing FDD procedures [29]. Besides, in another research, it was demonstrated that more than 98% of patients were within the optimal range with Multiplate® test after half-dose (30 mg) loading of prasugrel [30].

Although there are several ways of detecting platelet aggretation inhibition, Multiplate® test is used as resistance test in our center. Flechtenmacher *et al*. [28] compared antiplatelet resistance with LTA, VerifyNow and Multiplate® test in 97 patients who under-

went cerebrovascular stenting and found clopidogrel resistance to 47.6%, 50.5% and 35.9%, respectively. Accordingly, the highest resistance frequency was determined by VerifyNow test and the lowest resistance was reported by Multiplate® test. In the same study, the correlation between resistance results reported with LTA test and the risk of thromboembolic complications was found to be better than Multiplate® and VerifyNow tests. The LTA test is the gold standard for antiplatelet resistance; however, it is a time consuming test because of necessity to be used in a laboratory environment. The tests that can be performed patient-based are Multiplate® and VerifyNow. The VerifyNow test is widely used because it has the same principle as the LTA test and is a fully automated system. The Multiplate® test is a semi-automated system and can be performed at the bedside, such as VerifyNow, in the presence of trained stuffs [31].

As it can be understood from studies ever published, there is variability in the dose and duration of antiplatelet therapy and the cut-off values of antiplatelet resistance, as well as the patient population and stent indication in patients undergoing neurovascular procedure (Table 3). Therefore, it is inevitable that the frequency of resistance ranges in a wide variation. The general term is the presence of a group of patients in whom platelet inhibition is not sufficient despite dual antiplatelet therapy. However, there are usually single-center, retrospective studies investigating the prognosis in this patient group.

In our study, the frequency of detecting thromboembolic findings by radiological methods in patients with aspirin or clopidogrel resistance was lower in the resistant group but there was no statistically significant difference between the two groups. However, we reckon that the reason for the lower rate of thromboembolism in the resistant group is the change of medication in the patients who was with resistance to clopidogrel. Shim *et al*., in their meta-analysis, which reviewed the studies performed on patients undergoing neurosurgical procedures, emphasized that patients resistant to antiplatelet treatments had a higher risk of thromboembolic events than those with normal responses. They found stent placement was associated with thromboembolic risk in the resistant group in patients undergoing neurosurgical procedures. In addition, studies suggesting that re-regulated antiplatelet therapy regimens may help to reduce the risk of thromboembolic events in patients with resistance demonstrated by antiplatelet resistance test. However, due to the variable results between single-center studies, they emphasized that cautious approach should be taken among adjusting antiplatelet therapy with the results of antiplatelet resistance tests [32].

### Limitations

Our study has some limitations. The most important one is that it is a single-centered study. Hence, it reflects the frequency of drug resistance on a single region. In addition, the effect of aspirin and clopidogrel resistance on clinical outcomes could not be evaluated due to the regulation of medication after resistance was demonstrated and absence of a control group owing to retrospective design of the study.

## CONCLUSION

In conclusion, in this study the incidence of aspirin resistance was 9.4% and clopidogrel resistance was 23.8% in patients who underwent neurovascular stenting.The frequency of antiplatelet resistance is very variable among these patients, mainly due to variency in the patient population, stent indication, dose-duration of antiplatelet therapy administered and the tests used to determine antiplatelet resistance as well as the cut-off values of the tests. However, as it is seen in our study, there is a group of patients who do not have sufficient platelet aggregation inhibition despite antiplatelet therapy. For this reason, the resistant patient group can be determined by performing platelet inhibitation tests before the interventional procedure. The presence of antiplatelet resistance in these patients and the effect of individual-based antiplatelet therapy on clinical outcomes should be investigated in prospective randomized controlled trials.

*Authors' Contribution*

Study Conception: DA, HD, ŞO, MS; Study Design: DA, HD, ŞO, MS; Supervision: DA, HD, ŞO, MS; Funding: DA; Materials: DA; Data Collection and/or Processing: DA, HD, ŞO, MS; Statistical Analysis and/or Data Interpretation: DA, HD, ŞO, MS; Literature Review: DA, HD, ŞO, MS; Manuscript Preparation: DA, HD, ŞO, MS and Critical Review: DA, HD, ŞO, MS.

*Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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# Is red blood cell distribution width an indicator of prognosis and mortality in respiratory intensive care unit?

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## ABSTRACT

**Objectives:** The range of variation of erythrocytes measured as Red blood cell distribution width (RDW). Mortality indicators in patients in intensive care depend on variation of physiological variables. High RDW rates have been commonly associated with heart disease, pulmonary embolism and pulmonary hypertension, peripheral artery disease, heart failure, liver disease and infectious diseases. We aimed in this study to determine the effect of RDW on prognosis and mortality in Chronic Obstructive Pulmonary Disease (COPD) patients in intensive care unit (ICU).

**Methods:** The cases who are treated for COPD in ICU between January 1, 2018 and December 31, 2019 reviewed. Demographic data, Charlson Comorbidite Index (CCI), Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) scores, procalcitonin, white blood cell, RDW, C-reactive protein, duration of mechanical ventilation, inotrope requirement, length of stay ICU, and 30-day mortality reviewed.

**Results:** Total number of 369 cases are included into the study and divided in two groups according to their RDW values (High RDW and normal RDW group). High RDW group had longer length of stay in ICU and hospital, mechanical ventilation duration, higher APACHE II, CCI, SOFA, white blood cell and procalcitonin values and lower C-reactive protein compared to normal RDW group. First outcome was hospital 30-day mortality in ICU. The age, RDW, inotrope use, MV duration, LOS H, APACHE II, CCI, SOFA, procalcitonin, CRP, HGB and HCT levels were found to be higher in patients with mortality compared those without. With the sensitivity value of 70.9% and the specificity of 47.7%, RDW the cut off value was found to be 16.5.

**Conclusions:** The risk of 30-day mortality, length of stay ICU and hospital and mechanical ventilation duration was higher in COPD patients with high RDW levels.

**Keywords:** RDW, ICU, COPD, mortality, indicator

The range in the volume and size of the red blood cells are measured with the test named red cell distribution width (RDW) [1]. RDW is always included in the complete blood count panel and inexpensive to do. The normal range is 11.6-17.2%. Although RDW is traditionally used to differentiate the type of anema, in recent studies, high RDW rates are found to be associated with heart disease, heart failure, acute pulmonary embolism and pulmonary hypertension, peripheral artery disease, liver disease, and infectious diseases [2-7]. Additionally, the RDW values have also been shown to be high in other critically

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ill patients with pneumonia, Gr (-) bacteriemia, and sepsis in intensive care unit (ICU) and it was a risk factor for hospital mortality [8-11].

Metabolic abnormalities like oxidative stress and inflamation in the cells are linked to high RDW levels and might be the main cause of the mortality in critically ill patients [12]. Mortality indicators in patients admitted to ICU depend on many physiological variables.

This research is aimed to determine the prognostic value of RDW and its relationship with mortality in patients with Chronic Obstructive Pulmonary Disease (COPD) in intensive care.

## METHODS

The retrospective study was initiated after approval from the Medical Specialization Training Board of Ataturk Chest Diseases and Thoracic Surgery Training and Research Hospital (approval date & number: 12/17/2020 & 705).

The cases who were admitted to ICU between January 1, 2018 and December 31, 2019 were reviewed retrospectively. The study included patients aged 18 years and older, admitted to ICU with a diagnosis of COPD between January 1, 2018 and December 31, 2019.

Exclusion criteria were as follows; cases with

**Table 1. Demographics and prognostic factors of the patients according to RDW distribution**

| n =369 | | RDW (%) | | *p* value |
|---|---|---|---|---|
| | | Normal RDW (n = 216) | High RDW (n = 153) | |
| | | $\bar{X}$ ± SD / Median (IQR) | $\bar{X}$ ± SD / Median (IQR) | |
| Gender | Female | 84 (38.9%) | 55 (35.9%) | 0.566 |
| | Male | 132 (61.1%) | 98 (64.1%) | |
| Age (year) | | 72.76 ± 11.45 | 71.14 ± 11.17 | 0.178 |
| 30 day mortality | | 68 (31.5%) | 66 (43.1%) | **0.022** |
| Inotrope use | | 51 (23.6%) | 37 (24.2%) | 0.899 |
| LOS H (day) | | 15 (15) | 19 (16) | **0.009** |
| LOS ICU (day) | | 3(4) | 4 (7) | **0.016** |
| MV duration (day) | | 0 (2) | 0 (4) | **0.026** |
| APACHE II | | 20 (7) | 20 (11) | **0.046** |
| CCI | | 6 (3) | 6 (3) | **0.027** |
| SOFA | | 5 (2) | 5 (4) | **0.021** |
| WBC ($\times 10^3$/ml) | | 11 (6.9) | 12.4 (7.6) | **0.050** |
| Procalcitonin (ng/ml) | | 0.18 (0.64) | 0.29 (2.8) | **0.037** |
| CRP (mg/l) | | 33.84 (54.12) | 7.7 (21.83) | **0.015** |
| HGB (g/dl) | | 12.2 (3.35) | 11.3 (4) | 0.055 |
| HCT (%) | | 38.6 (11) | 37.7 (13.2) | 0.471 |

Continuous variables are expressed as either the mean ± standard deviation (SD) or the median (IQR ), and categorical variables are expressed as either $^{\delta}$ frequency or percentage. Continuous variables were compared with a student t test or the mann whitney u test, and categorical variables were compared using Pearson's chi-square test or fisher exact test. RDW = Red blood cell distribution width, LOS H = Length of stay Hospital, LOS ICU = Length of stay Intensive Care Unit, MV = Mechanical Ventilation, APACHE II = Acute Physiology and Chronic Health Evaluation II, CCI = Charlson Comorbidite Index, SOFA = Sequential Organ Failure Assessment, WBC = White blood cell, CRP = C-reactive protein, HGB = Hemoglobin, HCT = Hematocrit

known hematological malignancy, recent blood transfusion and anemia (hemoglobin < 13.5 g/dl in males, hemoglobin < 12.0 g/dl in females are accepted as anemia), cases who were stayed in ICU less than one day and cases who had a pathology or medical condition makes RDW lower than 11.6.

The normal range of RDW is 11.6-17.2, the cases with RDW ≥ 17.3 are included into the high RDW group.

Clinical data like demographics, Charlson Comorbidite Index (CCI), Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores, procalcitonin, white blood cell (WBC), C-reactive protein (CRP) values, length of stay ICU (LOS ICU), length of stay hospital (LOS H), mechanical ventilation (MV) duration, inotrope use, hemoglobin (HGB), hematocrit (HCT) and RDW values are noted. The mortality data has been taken from the Death Notification System.

## Statistical Analysis

The results were compared using Statistical Package for the Social Sciences, version 22.0 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous variables was normal or not was determined by Kolmogorov Smirnov test. Continuous data were described as mean ± SD and median (interquartile range) for skewed distributions. Categorical data presented as numbers and percentages. Categorical variables were compared using Pearson's chi-square test or fisher's exact test. Firstly, possible risk factors that thought to be related with mortality were analyzed in one variable multinominal logistic regression analyzed. Variables with $p < 0.25$ in univariate logistic regression analysis were included in multivariate logistic regression analysis. The Backward Wald method was used for multivariate logistic regression analysis. ROC curve analysis was used to determine the cut off points. The $p$ -value < 0.05 is accepted as significant

**Table 2. The factors affecting mortality in COPD patients**

| n = 369 | Univariate Analysis | | | | | Multivariate Analysis (Backward wald 6th step) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Wald | *p* value | OR | 95% CI for EXP(B) | | Wald | *p* value | OR | 95% CI for EXP(B) | |
| | | | | Lower | Upper | | | | Lower | Upper |
| Age (year) | 7.332 | **0.007** | 1.027 | 1.007 | 1.047 | | | | | |
| Gender | 0.306 | **0.580** | 1.132 | 0.729 | 1.758 | | | | | |
| RDW (%) | 5.822 | **0.016** | 1.076 | 1.014 | 1.141 | | | | | |
| LOS H (day) | 2.042 | **0.153** | 0.989 | 0.975 | 1.004 | 10.049 | **0.002** | 0.966 | 0.946 | 0.987 |
| LOS ICU (day) | 9.141 | **0.002** | 1.056 | 1.019 | 1.095 | | | | | |
| MV duration (day) | 20.847 | **< 0.001** | 1.111 | 1.062 | 1.163 | 11.650 | **0.001** | 1.081 | 1.034 | 1.130 |
| APACHE II | 45.444 | **< 0.001** | 1.130 | 1.090 | 1.170 | 10.350 | **0.001** | 1.073 | 1.028 | 1.121 |
| CCI | 19.046 | **< 0.001** | 1.295 | 1.153 | 1.455 | | | | | |
| SOFA | 67.431 | **< 0.001** | 1.751 | 1.532 | 2.001 | 30.189 | **< 0.001** | 1.519 | 1.309 | 1.763 |
| WBC($\times 10^3$/ml) | 0.138 | **0.710** | 0.997 | 0.983 | 1.012 | | | | | |
| Procalcitonin (ng/ml) | 0.647 | **0.421** | 1.006 | 0.991 | 1.021 | | | | | |
| CRP (mg/l) | 7.780 | **0.005** | 1.005 | 1.001 | 1.008 | 4.232 | **0.040** | 1.005 | 1.000 | 1.009 |
| HGB (g/dl) | 5.109 | **0.024** | 0.903 | 0.827 | 0.987 | | | | | |
| HCT (%) | 7.299 | **0.007** | 0.965 | 0.940 | 0.990 | 7.175 | **0.007** | 0.957 | 0.927 | 0.988 |

OR = odds ratio. Multinominal Logistic Regression Nagelkerke $R^2$=0.512 (Hosmer ve Lemeshow $p > 0.05$)

RDW = Red blood cell distribution width, LOS H = Length of stay Hospital, LOS ICU = Length of stay Intensive Care Unit, MV = Mechanical Ventilation, APACHE II = Acute Physiology and Chronic Health Evaluation II, CCI = Charlson Comorbidite Index, SOFA = Sequential Organ Failure Assessment, WBC = White blood cell, CRP = C-reactive protein, HGB = Hemoglobin, HCT = Hematocrit

**Table 3. The RDW cut-off value for mortality**

| Test variables: RDW | | | | | | |
|---|---|---|---|---|---|---|
| AUC | *p* value | 95% Confidence Interval | | Cut off | Sensitivity | Specifity |
| | | Lower | Upper | | | |
| 0.580 | **0.002** | 0.539 | 0.658 | 16.5 | 70.9% | 47.7% |

AUC = area under the curve

and *p* value between 0.05 and 0.10 are excepted borderline significant level on all statistical analysis.

## RESULTS

The comparison of the demographic, clinical and laboratory data of patients (n = 369) admitted to ICU with COPD, according to RDW groups are given in the Table 1. According to the results, 30-day mortality, LOS ICU, LOS H, MV duration, APACHE II, CCI, SOFA, WBC and procalcitonin values were found to be significantly higher and CRP levels were significantly lower in the group with high RDW values (Table 1).

Logistic regression analysis was done usin the possible factors that might affect mortality in cases with COPD. After the last step of the analysis (6$^{th}$ step), six parameters (LOS H, MV duration, APACHE II, SOFA, CRP and HCT) were found to be the significant determinators for hospital mortality in cases with COPD, treated in ICU. The increase in MV duration, APACHE II scores, SOFA scores and CRP values and decrease in LOS H and HCT values are associated with increase hospital mortality in cases with COPD (Table 2).

A ROC curve analysis was applied to find the RDW cut off value in cases with COPD that determines the success of the RDW value in predicting mortality. It shows that RDW can differentiate in determining the mortality risk at COPD patients correctly at a rate of 58% (moderate). To answer the question of which value should be taken as the cut-off value for this test, the sensitivity value was 70.9% and the specificity value was 47.7%, the cut off value was found to be 16.5. The risk of mortality was found statistically higher in patients with RDW of 16.5 and above (Table 3) (Fig. 1).

The age, RDW, inotrope use, MV duration, LOS H, APACHE II, CCI, SOFA, procalcitonin, CRP, HGB and HCT levels were found to be higher in patients with mortality compared to those without mortality (Table 4).

Spearman correlation analysis was applied to determine the relationship between RDW values and other variables of patients with COPD in intensive care and the results are given in the Table 5. Accordingly, there is a low level positive correlation between RDW and LOS H, LOS ICU, MV duration, APACHE II, CCI, SOFA, and WBC. There is a low level negative relationship between RDW and CRP, and HGB (Table 5).

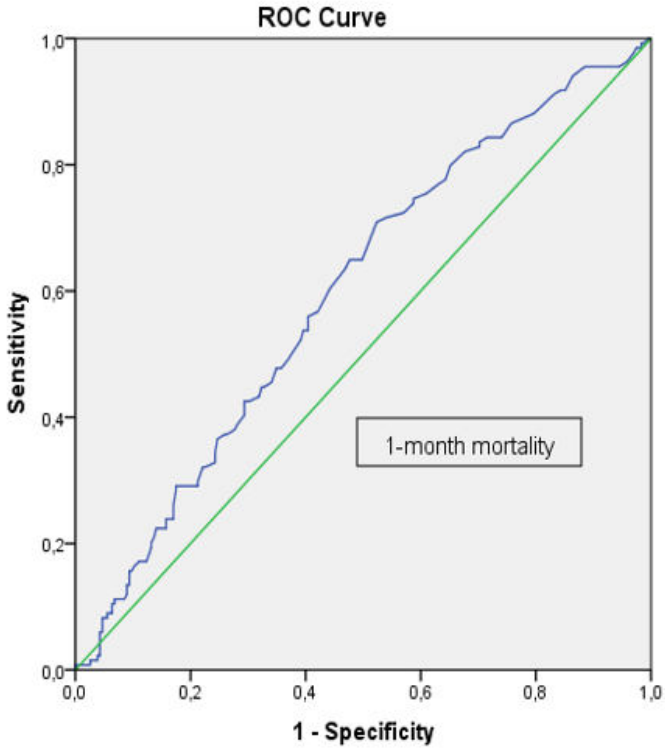


**Fig. 1. ROC Curve Analysis for RDW value in predicting mortality.**

**Table 4. Comparison between cases with and without mortality**

| n = 369 | Mortality (+) (n = 134) | Mortality (–) (n = 235) | *p* value |
|---|---|---|---|
| Sex, n (%) | | | 0.580 |
| Female | 48 (35.8%) | 91 (38.7%) | |
| Male | 86 (64.2%) | 144 (61.3%) | |
| Age (year) | 75 (15) | 71 (17) | **0.003** |
| RDW | 17.2 (4.32) | 16.2 (3.9) | **0.002** |
| Intrope use. n (%) | 70 (52.2%) | 18 (7.7%) | **< 0.001** |
| MV duration (day) | 3 (6) | 0 (0) | **< 0.001** |
| LOS ICU (day) | 4.5 (7) | 3 (4) | **0.003** |
| LOS H (day) | 17 (19) | 16 (15) | 0.235 |
| APACHE II | 24 (11) | 19 (6) | **< 0.001** |
| CCI | 7 (3) | 6 (3) | **< 0.001** |
| SOFA | 7 (4) | 4(2) | **< 0.001** |
| WBC ($\times 10^3$/ml) | 12.05 (6.85) | 11.5 (6.7) | 0.616 |
| Procalcitonin (ng/ml) | 0.31 (2.2) | 0.15 (0.71) | **0.002** |
| CRP (mg/l) | 17.4 (54.55) | 8 (25.79) | **0.002** |
| HGB (g/dl) | 12.2 (3.8) | 11.65 (3.4) | **0.039** |
| HCT (%) | 38.7 (12.4) | 37.1 (12) | **0.018** |

Continuous variables are expressed as the median (IQR ) and categorical variables are expressed as either frequency or percentage. Continuous variables were compared with the mann whitney u test and categorical variables were compared using Pearson's chi-square test or fisher exact test. RDW = Red blood cell distribution width, LOS H = Length of stay Hospital, LOS ICU = Length of stay Intensive Care Unit, MV = Mechanical Ventilation, APACHE II = Acute Physiology and Chronic Health Evaluation II, CCI = Charlson Comorbidite Index, SOFA = Sequential Organ Failure Assessment, WBC = White blood cell, CRP = C-reactive protein, HGB = Hemoglobin, HCT = Hematocrit

## DISCUSSION

In this study, we detected an association between RDW values and prognosis-mortality of patients with COPD in ICU. Our findings are as follows; firstly; 30-day mortality, LOS H, LOS ICU and MV duration are higher in patients with high RDW values compared to those with normal RDW. Secondly; RDW is moderately succesfull in determining the mortality risk at COPD patients, with an accuracy of 58 percent. Thirdly; RDW is found to be one of the predictor for mortality. The other predictors of mortality was older age, inotrope use, MV duration, LOS H, APACHE II, CCI, SOFA, procalcitonin and CRP levels.

Similarly to our study, Osadnik *et al*. [13] also found an association between RDW and mortality. They thought that this association was due to the positive correlation between RDW and inflammation [13].

In a study of Lorente *et al*. [14]; septic patients who died had higher RDW values compared to survivors in the the first week of ICU admission. They also found association between RDW and SOFA, COPD, ischemic heart disease [14]. In our study, we used CCI for defining comorbidities and found COPD patients with higher RDW levels had also higher 30-day mortality. Lorente *et al*. [14] showed that patients with RDW more than 15.5% had a 70% higher risk of death in the first 30 days than those with a lower RDW values.

Similar to our study, other researchers found that high RDW levels were a risk factor for mortality in patients with some certain medical conditions. RDW has been associated with increased mortality in inten-

**Table 5. The relation between RDW and other variables in COPD patients**

| | | RDW n = 369 |
|---|---|---|
| Age | r | -0.041 |
| | *p* | 0.438 |
| LOS H | r | 0.162 |
| | *p* | **0.002** |
| LOS ICU | r | 0.144 |
| | *p* | **0.005** |
| MV Duration | r | 0.170 |
| | *p* | **0.001** |
| APACHE II | r | 0.191 |
| | *p* | **< 0.001** |
| | n | **368** |
| CCI | r | **0.159** |
| | *p* | **0.002** |
| SOFA | r | **0.133** |
| | *p* | **0.011** |
| WBC | r | 0.114 |
| | *p* | **0.028** |
| Procalcitonin | r | 0.082 |
| | *p* | 0.118 |
| CRP | r | -0.116 |
| | *p* | **0.026** |
| HGB | r | -0.154 |
| | *p* | **0.003** |
| HCT | r | -0.060 |
| | *p* | 0.251 |

RDW = Red blood cell distribution width, LOS H = Length of stay Hospital, LOS ICU = Length of stay Intensive Care Unit, MV = Mechanical Ventilation, APACHE II = Acute Physiology and Chronic Health Evaluation II, CCI = Charlson Comorbidite Index, SOFA = Sequential Organ Failure Assessment, WBC = White blood cell, CRP = C-reactive protein, HGB = Hemoglobin, HCT = Hematocrit

sive care patients [8, 9], patients with community acquired pneumonia [10], sepsis [15], gram-negative bacteremia [11]. Sadaka *et al*. [16] studied in patients with septic shock; they found that high RDW was associated with higher mortality. However, Budak *et al*. [17] did not find a relation between RDW and other inflammation markers like MPV, NRL and WBC count.

Zhang *et al*. [18] found that high RDW levels were associated with mortality on admission; however its predictive performance was suboptimal. Similarly, this study showed that RDW might determine the mortality risk at COPD patients with an accuracy of 58%. There are some studies in the literature about relation with RDW and sepsis-mortality, but there is not enough study on COPD patients. Although RDW is shown as mortality indicator COPD patients in ICU, multicenter randomized studies with large number of the patients with other respiraory disease are required to confirm the role of RDW in prognosis of the pa-

tients in ICU.

### Limitations

Our study's limitations are as follows; a single-center study and has retrospective design, we measured RDW only in admission into the ICU therefore we can not comment on the RDW change by time and we have only included the patients with COPD and we might not generalize our findings to all patients with other respiratory diseases.

## CONCLUSION

The risk of 30-day mortality, LOS H, LOS ICU and MV duration was higher in COPD patients with high RDW levels but there is a low level correlation.

*Authors' Contribution*

Study Conception: GED, MÖC; Study Design: GED, MÖC; Supervision: GED, MÖC; Funding: GED, MÖC; Materials: GED, MÖC; Data Collection and/or Processing: GED, MÖC; Statistical Analysis and/or Data Interpretation: GED, MÖC; Literature Review: GED, MÖC; Manuscript Preparation: GED and Critical Review: MÖC.

*Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2021;7(6):617-627 Original Article

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# Assessment of neonatal sepsis and associated factors among neonates admitted neonatal intensive care unit in selected public hospitals in Somali region, Ethiopia

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## ABSTRACT

**Objectives:** To assess neonatal sepsis and associated factors among neonates admitted neonatal intensive care unit in selected public hospitals in Somali region, Ethiopia.

**Methods:** Institution based cross sectional study design was conducted in selected public hospitals. Data was collected using structured questionnaire adopted from other literature, entered into Epi-data version 3.1 and then was exported to SPSS version 23 for analysis. Frequency was used for descriptive analysis. Bivariate analysis was used to determine the association between different risk factors and the outcome variable. Those variables which have significant association at 5% significance level and fulfilling the minimum requirement of 0.2 level of significance with neonatal sepsis was entered for further analysis to multivariate analysis, significance was taken at $\alpha = < 0.05$.

**Results:** The overall prevalence of this study was 42.9% CI = (38.4-47.8) and associated factors was age of the neonate AOR = 0.085 (CI = 0.01, 0.73), Residence shown AOR = 2.567 (CI = 1.01, 6.5) Gestational age AOR = 1.869 (CI = 1.05, 3.31), Meconium stained Amniotic fluid AOR = 2.718 (CI = 1.89, 6.74), Antenatal care AOR = 8.933 (CI = 4.9, 15.9), and Mechanical ventilation after birth OR = 3.376 (CI = 1.65, 6.88).

**Conclusions:** The present study found that the overall prevalence of neonatal sepsis in selected hospitals was 42.9%. The study identified, Age of the neonate, Residence, Gestational age, Meconium stained amniotic fluid. Antenatal care, Mechanical ventilation after birth. The findings underscore the importance of routine assessment and close monitoring of neonates. It is therefore recommended to have more skilled health personnel and advanced equipment while providing maternal and new-born health care services.

**Keywords:** Neonatal sepsis, associated factors, neonates admitted neonatal intensive care unit, selected public hospitals, Somali region, Ethiopia 2017/2018.

Sepsis is defined as a clinical syndrome describe by a set of hemodynamic, respiratory and metabolic shifts secondary to an infectious process that can prompt an unusual systemic inflammatory response syndrome of the organism (SIRS) [1].

Neonatal sepsis is a defined as a clinical syndrome characterized by signs and symptoms of infection in an infant 28 days of life or younger. And it is a major cause of morbidity and mortality in newborns [2]. Early onset of neonatal sepsis defined as occurring in the first 3 days of life and is caused by bacterial pathogens transmitted vertically from mother to infant before or during delivery while late-onset sepsis (LOS) is sepsis occurring after 72 h in NICU infants

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and 7 days of life in term infants, has been variably defined as occurring up to the age of _90 or 120 days, and may be caused by vertically or horizontally acquired pathogens [3]. According to WHO the epidemiology of sepsis is better known in adults than in children, yet neonatal and child death due to sepsis is a major problem. There are an estimated 2.9 million deaths worldwide from sepsis every year (44% of them in children under 5 years of age) and one quarter of these is due to neonatal sepsis [4]. In 2012, an estimated 6.9 million (uncertainty range 5.5 – 8.3 million) possible severe bacterial infections occurred in neonates in Latin America, South Asia, and sub-Saharan Africa [5]. Neonatal sepsis is the third most common cause of death in this age group with an estimated 0.401 millions of deaths (uncertainty range [0.280-0.522], 6.8% [4.7-8.6]) in 2015, the vast majority of which are in developing countries [6].

Another report showed Globally the leading causes of death among children under age 5 included preterm birth complications (18%), pneumonia (16%), and intrapartum related events (12%), congenital anomalies (9%), diarrhea (8%), neonatal sepsis (7%) and malaria (5%) [7].

Based on the 2014 WHO/CHERG estimates for Ethiopia the major causes of children less than 5 years mortality, were acute respiratory infection (ARI) (18%), diarrhea (9%), prematurity (11%), sepsis (9%), birth asphyxia (14%), injuries (6%), and measles (2%) and others (21%) [8].

As it shows the 2016 Ethiopia Demographic and Health Surveys (EDHS), neonatal mortality declined from 49 deaths per 1,000 live births in 2000 to 29 deaths per 1,000 births in 2016, a reduction of 41% over the past 16 years and in Somali region is 41 deaths per 1000 live births [9].

Numerous factors associated with the high mortality due to infections were due to delays in the early identification and treatment of newborns with infection, particularly; under-recognition of illness, delay in care seeking at the household level, delay in initiation of treatment, and lack of access to both appropriately trained health workers and to high quality services to manage sepsis. It is particularly affecting that many neonatal deaths occur in the community, without the newborn ever having contact with the appropriate health care services [10, 11].

The third Sustainable Development Goal for child health (United Nations 2015), which aims to end preventable deaths of neonates and children under five years of age by 2030, may not be met without substantial reduction of neonatal sepsis-specific mortality in the developing countries [12].

In the world and especially sub-Saharan African countries Newborn survival is a problem of great concern, although Ethiopia made big efforts on maternal and child health programs and advancing healthcare system, most of the neonatal admission to the NICU with sepsis, has been increased. Many studies have been done in Ethiopia but there were limited studies tried to substantiate the risk factors of neonatal sepsis in the study areas (pastoral areas) of the country as a whole. This study was therefore, carried out to find out neonatal sepsis and factors contributing among neonates in three public hospitals of Somali region, Ethiopia.

## METHODS

### Study Area

This, study was conducted in Jigjiga, Godey, Kabri-dahar hospitals of Somali Region, Eastern Ethiopia from December-May2017/2018. Jigjiga town is the capital city of Somali regional state located 626 km east from Addis Ababa, capital city of Ethiopia & 101 km east from Harar town. As of 2009 EFY Jigjiga city has total population of 199,431 of which 45,570 are in reproductive age group (15-49 years). Current it has 30 Kebles of which 20 are urban & 10 are rural. Majority of people are Somali ethnic (97%) & Muslim in religion (98%). People of Jigjiga city are mostly agro-pastoral, their main source of income depends on farming and livestock, other source of income like small business, government employees etc. Jigjiga city has one Referral hospital, one Zonal hospital, two health centers & ten health posts, Two public hospitals and two health center are providing delivery service [13].

Godey Council is located in the Shebelle Zone of the Somali Region it is located 600 km away from Regional capital, Jigjiga (capital town of Ethiopian Somali region). It is Semi-arid weather condition and low altitude with flat land surfaces [14]. Administratively, it consists 10 Kebeles. Total population of the council is estimated to be 75,000 in 2016 (33,000 male and

42,000 females). In terms of health delivery system, the council has one Hospital, 1 NGO clinics and 4 Health Posts [15].

Based on figures from the Central Statistical Agency in 2005, Kabri-dahar has an estimated total population of 100,191 of whom 51,327 are men and 48,864 are women. The two largest ethnic groups reported in this town were the Somali (89.02%), and the Amhara (2.58%); all other ethnic groups made up 8.4% of the population. City has one zonal hospital and two health centers 2 heath posts [14].

## Study Design

An institution based cross-sectional study design was employed.

## Source Population

All neonates who were admitted to NICU of hospitals during the study period in Somali region were the study population for this study.

## Study Population

All new-born ≤ 28 days of life and who were admitted in neonatal ward randomly selected to involve in the study.

*Inclusion Criteria:* All neonates who were admitted to intensive care unit were included in this study.

*Exclusion Criteria:* Neonates who were early discharged before data collection was completed but only card was available, incomplete patient chart information, and died on arrival (neonates expired without taking any investigation and treatment on arrival) were excluded from this study.

## Sampling Procedure and sampling technique

There are nine regional hospitals in Somali region and three of them were selected by using lottery method (Fig. 1). The number of study subjects for each hospital was allocated proportionally after identifying the number of admissions in each hospital for the specified period (last three months). The number of admission in karamara was 5210; Gode hospital was 3460 and 1571 was Kabri-dahar hospital.

Proportionally allocated sample size of 203, 135 and 61 for karamara, Gode and Kabri-daharHospitals respectively. Participants' was selected consecutively

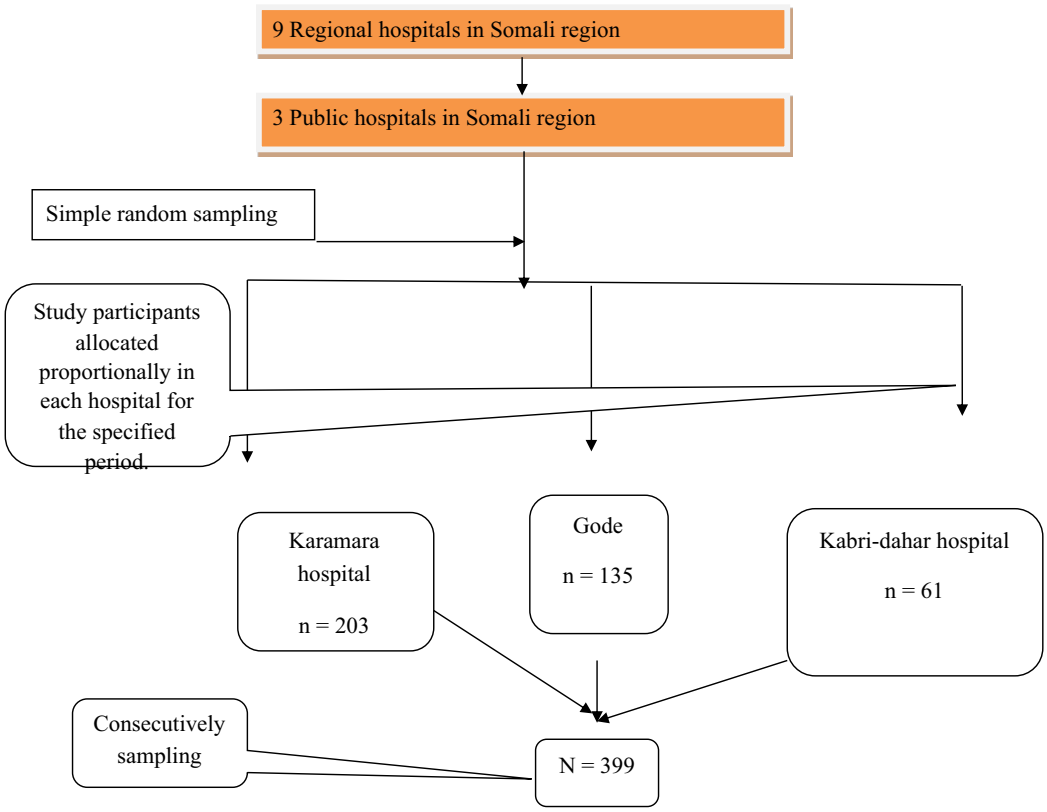


**Fig. 1. Sampling Procedure and sampling technique**

recruitment and was continued until the sample size allocated fulfilled/met.

### Data Collection Technique and Tools

A pre-tested interviewer-administered questionnaire and check lists were used to collect the data. The tools were developed by reviewing different literatures. The information was collected during the admission of neonate to NICU and by reviewing the registration book records in labor ward, NICU, and gynecologic ward in each hospital.

### Sample Size Determination

The sample size was determined by using single population proportion formula and the proportion was taken from the previous literature in Ethiopia. According to study conducted at Black Lion specialized hospital, the prevalence of neonatal sepsis was 44.7% and by considering 95% confidence interval (CI) and 5% marginal error the, sample size was calculated as follows:

$$\text{Where } n = (Z_{\partial/2})^2 \frac{P(1-p)}{d^2}$$

n = required sample size

Z = the standard normal deviation at 95% confidence interval; =1.96

P = prevalence of neonatal sepsis among neonates admitted in NICU with prevalence of 44.7% (16).

d= margin of error that can be tolerated, 5% (0.05)

1-p = proportion of population that do not possess the character of interest.

Therefore,

n = (Z∂/2)2 p (1 − p)/d2 = (1.96)2 (0.447) (0.553)/ (0.05)2= 380

By adding non response rate 5%, our total sample size was 399 neonates.

### Study Variables

*Dependent Variable:* Neonatal sepsis

*Independent Variable:* Socio-demographic characteristics of mothers, socio-demographic characteristics of neonates, and obstetric characteristics of mothers were independent variables for this study.

### Data Quality Control

Three training was given for two data collectors in each hospital with an academic background of diploma/degree in nursing/midwifery working outside the study hospitals The training was focused on introducing the data collection tools, the initial and end of the data collection period, how they are collected the data, using the time wisely, data handling, and submit the collected data. Pretest was done 5% to pave the way any solution/modification in appropriate time. Data completeness was checked, cleaned and compiled by the investigator on daily basis.

### Operational Definition

*Neonatal Sepsis:* neonate with sepsis within 0-28 days of life

*Early Onset Neonatal Sepsis:* neonate with sepsis within 0-7 days

*Late Onset Neonatal Sepsis:* neonate with sepsis within 8-28 days

*Low Birth Weight:* weight of the child

### Ethical Consideration

Ethical clearance letter was acquired from ethical Review Board of Jigjiga University, and after explaining about the purpose and the possible benefit of the study permission to gather datawas secured from regional health bureau and delivered to public hospital administrators. Confidentiality was maintained at all levels of the study.

### Statistical Analysis

The data was cleaned for inconsistencies and missing values and modification was considered as necessitate, coded and entered into Epi-data version 4.1 and then was exported to SPSS (Statistical Package for Social science) version 20 for analysis. Frequency was used for the descriptive, after assessing the normality of distribution of the data; Bivariate and multivariate analyses were used to assess the association between each independent variable and the outcome variable by using binary logistic regression. All variables with $P < 0.25$ in the Bivariate analysis were included in the final model of multivariate analysis in order to control all possible confounders. The degree of association between dependent and independent variables was examined using odds ratio with 95% CI. P-value less than 0.05 was considered as significance level for associations between dependent and independent variables. Confidence interval of 95% was

used to be examined the precision of the study and the level of significance was taken at α = < 0.05. Finally, result was presented in Texts, and Tables.

## RESULTS

### Socio-demographic Characteristics

A total of 380 neonates were involved in the study, with 95% response rate from December 2017 to May 2018 in three selected public hospitals (Karamara, Gode, Kabridahar). Regarding residence 340 (89.5%) resided urban, and 193 (50.8) of those were male and 61 (37.4%) developed neonatal sepsis. Concerning age of the neonates 365 (96.1%) aged between 0-7 days among these 149 (91.4%) developed neonatal sepsis, regarding maternal age 160 (42.1%) and 85 (52.1%) their neonates developed neonatal sepsis, Maternal education 274 (72.1%) of the mothers had never go to school, 114 (69.9%) of then had NS (Table 1).

### Prevalence of Neonatal Sepsis

This study, the prevalence and associated risk factors of neonatal sepsis of neonates admitted in the three selected hospitals with in the December-May 2017/2018. The total prevalence of this study was 42.9%, with CI = (37-46) (Table 2).

### Neonatal Characteristics

In terms of birth weight of the neonates, 286 (75.3%) of them had normal birth weight (< 2.5kg) and of these 139(85.3%) had EONS. Regarding gestational age 210 (55.3%) were term deliveries 102 (62.6%) had neonatal sepsis. About the Apgar score 323 (85%) had >7said to have Apgar score less than 7. About 225 (67.1%) of neonates who were reported as to have birth asphyxia, 102 (62.6%) of them developed neonatal sepsis (Table 3).

### Maternal Characteristics

Among 206 (54.2%) neonates who had history of maternal UTI and developed NS were 77 (47.2%) during delivery and 151 (39.7%) had maternal history of ANC follow up, among these 113 (69.3) had neonatal sepsis, about 49 (12.9%) of the mothers of the neonates had premature rupture of membrane and 24 (14.7%) developed neonatal sepsis, 26 (81.3%) duration < 18 hours. Regarding meconium stained amni-

**Table 1. Socio-demographic Characteristics**

| S/N | Variables | Category | Neonatal sepsis | |
|---|---|---|---|---|
| | | | Yes | No |
| | | | Number (%) | Number (%) |
| 1 | Residence | Urban | 138 (84.7) | 202 (93.1) |
| | | Rural | 25 (15.3) | 15 (6.9) |
| 2 | Sex of the neonate | Male | 61 (37.4) | 132 (60.8) |
| | | Female | 102 (62.6) | 85 (39.2) |
| 3 | age of the neonate | 0-7days | 149 (91.4) | 216 (99.5) |
| | | 8-28 days | 14 (8.6) | 1 (0.5) |
| 4 | Maternal age | < 19years | 16 (9.8) | 75 (34.6) |
| | | 20-30years | 85(52.1) | 75(34.6) |
| | | 30-40years | 52(31.9) | 57(26.3) |
| | | > 41 years | 10 (6.1) | 10 (4.6) |
| 5 | Maternal education | Never go to school | 114 (69.9) | 160 (73.7) |
| | | Primary | 45 (27.6) | 48 (22.1) |
| | | High school and above | 4 (2.5) | 9 (4.1) |
| 6 | Parity | Nulliparous | 36 (22.1) | 112 (51.6) |
| | | Multiparious | 127 (77.9) | 105 (48.4) |

**Table 2.** **Prevalence of neonatal sepsis**

| Variable | Category | Frequency | Percent |
|---|---|---|---|
| 7. Neonatal sepsis | Yes | 163 | 42.9 |
| | No | 217 | 57.1 |

otic fluid 60 (15.8%) of the mothers had MSAF and 14 (8.6%) during delivery and 14 (8.6%) developed neonatal sepsis. Regarding duration of labor 255 (67.1%) labored between 6-12 hours of these103 (63.2%) had NS (Table 4).

### Medical Related Factors

Regarding mode of delivery about 275 (72.4%) delivered spontaneously and 117 (71.8%) had neonatal sepsis and also 305 (80.3%). About 154 (40.5%) were resuscitated by mechanical ventilation, 106 (65%) developed neonatal sepsis (Table 5).

### Multivariate Analysis of the Association between Neonatal Sepsis and Other Neonatal Variables

In this study both Bivariate and multivariate level of analysis was investigated to determine the association between late onset neonatal sepsis and other different

**Table 3.** **Neonatal characteristics**

| S/N | Variables | Category | Neonatal sepsis | |
|---|---|---|---|---|
| | | | Yes | No |
| | | | Number (%) | Number (%) |
| 8 | Birth weight | < 2.5kg | 24 (14.7) | 23 (10.6) |
| | | 2.5-4kg | 139 (85.3) | 194 (89.4) |
| 9 | Gestational age | < 37weeks | 61 (37.1) | 109 (50.2) |
| | | > 37weeks | 102 (62.6) | 108 (49.8) |
| 10 | Apgarscore < 7 | < 7 | 22 (13.5) | 35(16.1) |
| | | > 7 | 141 (86.5) | 182 (83.9) |
| 11 | Birth asphyxia | Yes | 102 (62.6) | 153 (70.5) |
| | | No | 61 (37.4) | 64 (29.5) |
| 12 | Not breast feeding | Yes | 98 (60.1%) | 138 (63.6%) |
| | | No | 65 (39.9%) | 79 (36.4%) |
| 13 | Neonatal fever | Yes | 78 (47.9%) | 99 (45.6%) |
| | | No | 85 (52.1%) | 118 (54.4%) |

**Table 4.** **Maternal characteristics**

| S/N | Variables | Category | Neonatal sepsis | |
|---|---|---|---|---|
| | | | Yes | No |
| 14 | Maternal UTI | Yes | 77 (47.2) | 129 (59.4) |
| | | No | 86 (52.8) | 88 (40.6) |
| 15 | ANC | Yes | 113 (69.3) | 38 (17.5) |
| | | No | 50 (30.7) | 179 (82.5) |
| 16 | History of chorioamnionitis | Yes | 9 (37.5) | 154 (43.3) |
| | | No | 15 (62.5) | 202(56.7) |
| 17 | PROM | Yes | 24(14.7) | 25(11.5) |
| | | No | 139(85.3) | 192 (88.5) |
| 18 | If yes duration | <18hrs | 13 (76.5) | 13 (86.7) |
| | | >18hrs | 4 (23.5) | 2 (13.3) |
| 19 | MSAF | Yes | 14 (8.6) | 46 (21.2) |
| | | **No** | 149 (91.4) | 171 (78.8) |
| 20 | Duration of labour | < 6hours | 59 (36.2) | 63 (29) |
| | | 6-12hrs | 103(63.2) | 152 (70) |

risk factors. Variables those have significant association on Bivariate analysis was taken to multivariate analysis to control the confounders. The current study found that age of the neonate found to be significantly associated with neonatal sepsis, neonates aged 8-28 days were protective by 91% compared to neonates aged 0-7 days. AOR= 0.085 (CI= 0.01, 0.73) (Table 6). Regarding the residence, neonates who were from urban residence were 2.5 times more likely to develop neonatal sepsis compared to neonates from rural residence. AOR=2.567 (CI=1.01, 6.5). Gestational age, neonates who gestational age were < 37 weeks of gestation were 1.8 times more likely to develop neonatal sepsis compared to neonates who gestational age were 37-42 weeks AOR= 1.869 (CI= 1.05, 3.31). Concerning antenatal care, neonates who's their mother had not history of ANC were 8.9 times more likely to develop neonatal sepsis compared to neonates who's their mother had history of ANC flow up AOR= 8.933 (CI= 4.9, 15.9). Neonates who's their mother had meconium stained amniotic fluid were 2.7 times more likely to develop neonatal sepsis compared to neonates who's their mother had not meconium stained amniotic fluid AOR= 2.718 (CI= 1.89, 6.74). About ventilation, neonates who had mechanical ventilation were 3.3 times more likely to develop neonatal sepsis compared to neonates who had not mechanical ventilation after birth AOR= 3.376 (CI =1.65, 6.88) (see Table 6).

## DISCUSSION

This study, the prevalence and associated risk factors of neonatal sepsis of neonates admitted in the three selected hospitals with in the December-May 2017/2018. The total prevalence of this study was 42.9%,with CI =(38.4-47.8) this was near to compared to study conducted in Black lion specialized hospital in 2010 which was 44.7% [16]. And also to different studies in different countries showed very close figures India 35.1% Saudi Arabia (37%), Nigeria 33.1% Tanzania (31.4%) [17-20]. But its large different study finding in Mexico this could be due to the difference in study design, and the sample size which shown 4.3 % considerable low when compared other studies. This difference may have been contributed by the presence of more skilled personnel in Mexico and advanced or modernized equipment compared to other studies [21].

The current study found that age of the neonate found to be significantly associated with neonatal sepsis, neonates aged 8-28 days were protective by 91. % compared to neonates aged 0-7 days. AOR= 0.085 (CI= 0.01, 0.73) compared to Study conducted in Nigeria showed almost similar significance < 3 days compared to above these days above. the possible explanation of the difference can be the sample included who were age of less than three days [22]. This could

**Tablo 5. Medical related factors**

| S/N | Variables | Category | Neonatal sepsis | |
|---|---|---|---|---|
| | | | Yes | No |
| | | | Number (%) | Number (%) |
| 21 | Mode of delivery | Spontaneous | 117 (71.8) | 158 (72.8) |
| | | C/S | 15 (9.2) | 25 (11.5) |
| | | Instrumental | 31 (19) | 34 (15.7) |
| 22 | Place of delivery | Hospital | 124 (76.) | 181 (83.4) |
| | | Health center | 30 (18.4) | 30 (13.8) |
| | | Clinics | 2 (1.2) | 1 (0.5) |
| | | Health center | 7 (4.3) | 5 (2.3) |
| 23 | Mechanical ventilation | Yes | 23(20.5) | 140 (52.2) |
| | | No | 89 (79.5) | 128 (47.8) |

**Table 6. Multivariate analysis of the association between NS and other neonatal variables**

| Variables | Category | Neonatal sepsis | | | | |
|---|---|---|---|---|---|---|
| | | Neonatal sepsis | | COR (CI: 95%) | AOR [95%CI] | *p* value |
| | | Yes | No | | | |
| Sex of the neonate | Male | 61 | 132 | 2.5 (1.70, 3.94) | 1.519 (0.87, 2.63) | 0.127 |
| | Female | 102 | 85 | 1 | 1 | |
| Age of the neonate | 0-7days | 63 | 173 | 1 | 1 | |
| | 8-28 days | 100 | 44 | 0.16 (0.10, 0.25) | 0.085 (0.01, 0.73) | **0.025** |
| Maternal age | < 19 years | 16 | 75 | 4.68(1.67, 13.1) | 2.504 (0.64,9.7) | 0.186 |
| | 20-30 years | 85 | 75 | 0.88 (0.34, 2.23) | 0.930 (0.30, 2.80) | 0.897 |
| | 30-40 years | 52 | 57 | 1.09 (0.42, 2.84) | 1.06 (0.34, 3.24) | 0.919 |
| | > 41 years | 10 | 10 | 1 | 1 | |
| Parity | Nulliparous | 36 | 112 | 3.7 (2.38, 5.93) | 1.79 (0.85, 3.76) | 0.123 |
| | Multiparious | 127 | 105 | 1 | 1 | |
| Residence | Urban | 138 | 202 | 2.44 (1.24, 4.8) | 2.567 (1.01, 6.5) | **0.047** |
| | Rural | 25 | 15 | 1 | 1 | |
| Gestational age | < 37weeks | 61 | 109 | (1.15, 2.55) | 1.869 (1.05, 3.31)* | 0.032 |
| | 37-42 weeks | 102 | 108 | 1 | 1 | |
| Birth asphyxia | Yes | 102 | 153 | 1.43 (0.92, 2.20) | 0.943 (0.53, 1.66) | 0.840 |
| | No | 61 | 64 | 1 | 1 | |
| Maternal UTI | Yes | 77 | 129 | 1.63 (1.08, 2.4) | 1.287 (0.73, 2.25) | 0.376 |
| | No | 86 | 88 | 1 | 1 | |
| ANC | Yes | 113 | 38 | 1 | 1 | |
| | No | 50 | 179 | 10.6(6.56, 172) | 8.933(4.9, 15.9) | **< 0.001** |
| MSAF | Yes | 14 | 46 | 2.86 (1.5, 5.4) | 2.718 (1.89, 6.74) | **0.031** |
| | **No** | 149 | 171 | 1 | 1 | |
| Mechanical ventilation | Yes | 23 | 140 | 4.23 (2.52, 71) | 3.376 (1.65, 6.88) | **0.001** |
| | No | 89 | 128 | 1 | 1 | |

be due neonates with smaller ages had low immunity compared to those aged greater than first week of life. This difference might be due to the nature of age transfer as the physiologic events and changes associated with it.

Regarding the residence, neonates who were from urban residence were 2.5 times more likely to develop neonatal sepsis compared to neonates from rural residence. AOR= 2.567 (CI= 1.01, 6.5) this may be most of the neonates from urban residence were born health facility and they might acquire the nosocomial infection. Other thing is that some of the neonates were living urban slum areas where hygiene and sanitation, maternal and child health services are most commonly low.

Gestational age, neonates who gestational age were < 37 weeks of gestation were 1.8 times more likely to develop neonatal sepsis compared to neonates

who gestational age were 37-42 weeks AOR= 1.869 (CI= 1.05, 3.31).Compared to other studies also revealed Preterm delivery as significant risk factors for neonatal sepsis and in fact this factors has been well documented in previous studies [16, 23], In similar study conducted in Bishoftu city indicated that, preterm neonates did not showed significant association with the occurrence of neonatal sepsis [24] this may be due to health care service available or similarity of the design of the study used.

Concerning antenatal care, neonates who's their mother had not history of ANC were 8.9 times more likely to develop neonatal sepsis compared to neonates who's their mother had history of ANC flow up AOR= 8.933 (CI= 4.9, 15.9).This was consistent with study done in Uganda which showed that lack of ANC was significantly associated with neonatal sepsis. Thus Antenatal care is predictor to neonatal sepsis and it suggests to increase the awareness and strength maternal reproductive health utilization including this very important care during pregnancy [25].

The presence of meconium stained amniotic fluid is a significant predictor of neonatal infection to this study, Neonates whose their mother had meconium stained amniotic fluid were 2.7 times more likely to develop neonatal sepsis compared to neonates who's their mother had not meconium stained amniotic fluid AOR= 2.718 (CI= 1.89, 6.74).

Slightly more than this, studies conducted in Ghana displayed neonates who's their mother had meconium stained amniotic fluid were 3.6 times more likely to develop neonatal sepsis AOR= 3.60 (CI=1.73, 8.1) [26]. Other studies done in Ethiopia and Mexico agreed that specifically women who had meconium stained amniotic fluid were more likely to give birth to infants who suffered from neonatal sepsis compared to those without meconium stained amniotic fluid [23, 27]. There is also evidence supporting that when there ismeconium in amniotic fluid there is a greaterchance of the fetus being born with low Apgarscore, which unfortunately has earlier beenassociated with neonatal sepsis [16]. Normally it isexpected that the amniotic fluid should remain clear, however, in times of fetal hypoxia, it could be stained with meconium.

About ventilation, neonates who had mechanical ventilation were 3.3 times more likely to develop neonatal sepsis compared to neonates who had not mechanical ventilation after birth AOR = 3.376 (CI =1.65, 6.88) Similar result of study conducted in Mexico revealed that mechanical ventilation was predictor to neonatal sepsis [23]. These similarities may be due deficiency of knowledge among some of the health care providers on aseptic precautions while resuscitating neonates in all settings.

## CONCLUSION

The prevalence of neonatal sepsis in this study at selected public hospitals in Somali region is high. Study found that, the total prevalence of neonatal sepsis in selected hospitals was 42.9%, with CI = (38.4-47.8). The study identified Age of the neonate, Gestational age, Meconium stained amniotic fluid, antenatal care, Mechanical ventilation after birth as significant factors associated with neonatal sepsis. These findings suggest a possibility for routine assessment of neonates in order to identify risk factors for neonatal sepsis.

## RECOMMENDATİONS

*Policy Makers General*

Based on the result the policy makers must It is therefore recommended to have more skilled health personnel and advanced equipment while providing maternal and neonatal health care services and the overall public health services more significantly health promotion and making available each laboratory equipment necessary.

*For Regional Health Bureau*

It must be focus on the prevention of risk factors rather than treating the disease after it occurs by planning necessary training program for health professionals who works in pediatrics and neonatal ward in these hospitals that helps them to improve their knowledge regarding the problem and strength maternal and child health services and making accessible each laboratory equipment necessary.

*For Health Professionals*

Based on the study finding, create awareness to the community by giving health education to mothers about different risk factors of sepsis during of ANC

follow up which help them to screened and treated early. And when using treatment for neonatal sepsis they must consider the risk of misdiagnosis and mismanagement.

*Authors' Contribution*

Study Conception: AN; Study Design: MO; Supervision: MO; Funding: AN; Materials: AN; Data Collection and/or Processing: AN; Statistical Analysis and/or Data Interpretation: AN; Literature Review: MO; Manuscript Preparation: AN and Critical Review: MO.

*Conflict of interest*

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# The effect of neutrophil-lymphocyte ratio on admission to postoperative intensive care and mortality in elderly patients undergoing hip fracture surgery with spinal anesthesia

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## ABSTRACT

**Objectives:** Hip Fractures (HF) affect the elderly in particular, and are associated with high mortality rates. Most geriatric patients are admitted to Intensive Care Unit (ICU) after HF surgery. In this study, the purpose was to investigate the prognostic value of preoperative NLR (Neutrophil-to-Lymphocyte Ratio) on postoperative ICU admission and mortality in elderly patients with HF.

**Methods:** In the present study, the data of 188 geriatric patients who underwent surgery because of isolated HF (i.e. femur neck and intertrochanteric fracture) were examined retrospectively. The patients over 65 years of age, ASA score 3/4, whose preoperative duration was less than 72 hours, and who underwent spinal anesthesia were included in the study. The patients were divided into two groups as ICU admission (ICU, n = 58), and Non-ICU (Non-ICU, n = 130). The patients were also grouped as Survival (n = 168) and Non-survival (n = 20) according to postoperative mortality rates. NLR values were statistically compared between the groups.

**Results:** The preoperative NLR values of the patients in the ICU Group were significantly higher than those in the Non-ICU Group ($p < 0.001$). The cut-off value of NLR for ICU admission was found to be 9.65 with 89% sensitivity and 67% specificity in the ROC analysis. The median NLR value was 6.42 (3.55-9.44) in the Survivor Group, and 9.5 (7.23-11.02) in the Non-Survivor Groups ($p = 0.015$).

**Conclusions:** It was shown in the study that high NLR values in elderly patients may be a risk factor for ICU admission, and for postoperative mortality after HF.

**Keywords:** Geriatrics; hip fracture; neutrophil-to-lymphocyte ratio; intensive care unit; mortality

The population of the world is aging rapidly, and the number of Hip Fractures (HF) is increasing at the same rate. HF is a serious injury affecting the elderly in particular, and causes high mortality and morbidity. The mortality rate of patients after HF is approximately 15-20% [1-3].

Most of deaths following HFs are caused by cardiovascular events, such as heart failure, myocardial infarction, pulmonary thromboembolism, and infectious complications [1, 2]. It is seen that these high-risk patients, who are older and have comorbidities, are often admitted to ICUs whether in a planned or in an unexpected way according to their peroperative clinical status after HF surgery [3]. However, it is also known that patients who are admitted directly to the ICU in the postoperative period have better results

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compared to those who are not [4]. For this reason, the planned admission of patients to ICU help to prevent negative complications, minimizing the likelihood of adverse outcomes [4]. No standard protocol was detected in the literature that will guide the decision of these patients for admission to ICUs. The decision for admitting a patient to ICU is complex, and it is important to identify preoperative predictors that will affect this decision.

Some laboratory findings, such as high urea/creatinine, high glucose, high potassium, low hemoglobin and low albumin were shown in clinical trials to be associated with increased mortality and admission to ICUs in patients with HF [5-7]. It was also reported that inflammation markers, such as C-Reactive Protein (CRP) are associated with mortality [8]. Neutrophil-Lymphocyte Ratio (NLR) is an easily measured, inexpensive and widespread hematological parameter, which can be used as an indicator of systemic inflammation [8-10]. It has been argued in recent years that NLR can be used as an indicator of postoperative mortality and poor prognosis in oncological and emergency abdominal surgeries [9]. It has also been shown that preoperative NLR is the predictor of negative outcomes and mortality following HF surgery in orthogeriatric patients [1, 8, 10].

Identifying patients who have the highest risk of life-threatening complications in the preoperative period is important in preventing the onset of postoperative negative outcomes. As a hematological parameter, the NLR value can help as a guide to the clinician in the controversial ICU admission decision after hip surgery. For this reason, in the present study, the purpose was to investigate the prognostic value of preoperative NLR on postoperative ICU admission and mortality rates in elderly patients undergoing hip fracture surgery with spinal anesthesia.

## METHODS

### Study Design

The present study was conducted by retrospectively examining the files of geriatric patients who underwent surgery because of isolated HF (e.g. femur neck and intertrochanteric fracture) in the Orthopedic Clinic of our hospital between January 2017 and May 2019.

The inclusion criteria of the study were being over 65 years of age, ASA score 3/4, spinal anesthesia, and less than 72 hours preoperative duration. Exclusion criteria of the study were being under 65 years of age, under general anesthesia, having hematological, infectious and inflammatory disease, history of severe liver disease and malignancy, intraoperative mortality, revision surgery, multitrauma patients, and incomplete records.

### The Patients

ASA score, intervention time, surgery duration, and preoperative laboratory parameters (NLR) of the patients were evaluated. The surgery duration was calculated by adding the anesthesia procedure to the duration of the surgical procedure. The time to operation was defined as the day from hospitalization to surgical intervention.

The patients who were operated under regional anesthesia were included in the study. The patients were divided into two groups as those admitted to ICU (ICU), and those who were not (Non-ICU). The decision to admit to ICU was made by the anesthesiologist according to the peroperative clinical condition of the patient. Also, the duration of the stay in ICU and postoperative mortality of the patients were recorded. The patients were also divided further into two groups as the Survivor and Non-Survivor Group according to Intensive Care Unit mortality. The first admissions of all the patients who were admitted to ICU were accepted. All patients were routinely consulted for medical departments (cardiology, respiratory disease or internal medicine) in the preoperative period.

### Laboratory Measurements

Venous blood samples (full blood count (CBC)) that were taken from each patient at the Emergency Department were examined. All venous blood samples were processed by the Blood Analyzer (Beckman Coulter®, LH 780, California, USA). The ratio between neutrophil and lymphocyte values was calculated and recorded as NLR.

### Ethical Declaration

This retrospective study was approved by the Local Committee for Clinical Research in line with the Helsinki Declaration (Date: 24.07.2019, No: 2019/141).

### Statistical Analysis

Admission and mortality groups of ICU were statistically compared in terms of preoperative NLR value. Statistical analysis was performed using SPSS V.21 and MedCalc V.13 package. The significance level was described as $p < 0.05$. The descriptive statistics were given as mean, standard deviation, median, number and percentage. The Kolmogorov–Smirnov test was used to assess the normal distribution of the variables. Non-parametric parameters were analyzed using the Mann-Whitney U test. To determine the cut-off values of the NLR between the ICU and Non-ICU groups, a receiver operating characteristic (ROC) curve was generated, and the area under curve (AUC) was calculated.

## RESULTS

Among the 250 patients who were operated with HF diagnosis during the study period, 188 patients who met the inclusion criteria were included in the study for statistical analyses. A total of 111 (59%) of the patients were female, and the median age (min-max) of all patients was 78 (65-103) years; and 58 patients (30.9%) were included in the ICU Group and 130 patients (69.1%) were included in the Non-ICU Group. The median age of the patients was 79 (65-96) for the ICU Group, and 78 (66-103) for the Non-ICU Group ($p > 0.05$). A total of 168 patients (89.4%) were included in the Survivor Group and 20 patients (10.6%) were included in the Non-Survivor Group. The median age of the patients was 78 (65-94) for the Survivor Group, and 78 (65-103) for the Non-Survivor Group ($p > 0.05$) (Table 1).

Homogeneity was found between the groups, the mean age, gender, ASA score, and time to operation did not differ at significant levels between the groups ($p > 0.05$) (Table 1).

The preoperative NLR values of the patients in the ICU Group were significantly higher compared to those of the Non-ICU Group ($p < 0.001$). The median NLR value was calculated to be 7.59 (4.75-10.43) for the ICU-Group and 4.45 (2.29-7.86) for the Non-ICU Group (Table 2). The cut-off NLR was obtained according to the differences between the ICU and Non-

**Table 1. Demographic and clinical data of patients**

| Variables | ICU group | Non-ICU group | *p* value | Survivor group | Non survivor group | *p* value |
|---|---|---|---|---|---|---|
| Age (years) | 77.25 ± 7.5 | 78.5 ± 7.6 | 0.428[a] | 78.1 ± 7.5 | 78.3 ± 8.37 | 0.920[a] |
| Sex (female), n (%) | 35 (60.3) | 76 (58.5) | 0.808[b] | 102 (60.7) | 9 (45.0) | 0.177[b] |
| ASA score, n (%) | | | 0.694[b] | | | 0.118[b] |
| 3 | 27 (46.6) | 79 (60.8) | | 98 (58.3) | 8 (40) | |
| 4 | 31 (53.4) | 51 (39.2) | | 70 (41.7) | 12 (60) | |
| Time to operation (days) | 2.33 ± 1.7 | 2.24 ± 1.6 | 0.899[a] | 2.19 ± 1.6 | 2.85 ± 1.7 | 0.073[a] |

Data are presented as mean±standard deviation for continuous variables and number and percentage for categorical variable.
[a]Compared by Independent Sample T-Test; [b]Chi-square test

**Table 2. The neutrophil-lymphocyte ratio value of each group (Admission to ICU)**

| Group | Median | Interquartile range 25 | Interquartile range 75 | *p* value* |
|---|---|---|---|---|
| ICU group (n = 130) | 7.59 | 4.75 | 10.43 | **< 0.001** |
| Non-ICU group (n = 58) | 4.45 | 2.29 | 7.86 | |
| Total (n = 188) | 6.99 | 3.79 | 9.68 | |

*Compared by Mann Whitney U Testi

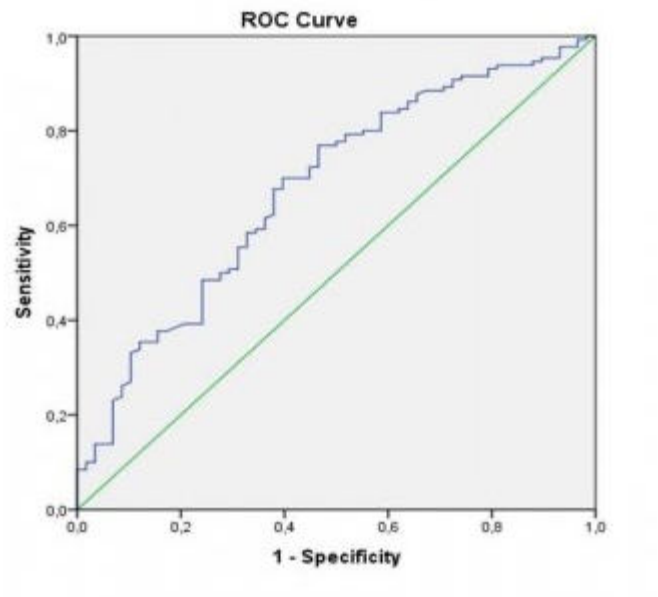


**Fig. 1. Sensitivity and specificity assessment with ROC curve of the relationship between neutrophil-lymphocyte ratio and admission of ICU.**

ICU Group by using the ROC Analysis. For ICU admission NLR, the cut-off point was determined as 9.65 (AUC of 0.67 [95 % CI 0.59-0.76] with 89% sensitivity and 67% specificity ($p < 0.001$)) (Fig. 1).

When the NLR values of the patients were compared according to intensive care mortality of the patients, significant differences were detected ($p < 0.05$). The Survivor Group had a median NLR value of 6.42 (3.55-9.44), and the Non-Survivor Group had a median NLR value of 9.5 (7.23-11.02) ($p = 0.015$) (Table 3).

## DISCUSSION

In the present study, the prognostic value of preoperative NLR value on ICU admission and mortality was examined in geriatric patients who underwent HF surgery. The results of our study showed that higher NLR value was associated with ICU admission and postoperative mortality after HF in elderly patients.

In elderly patients, hip fractures are among the most common traumatic diseases [1-3], which can cause postoperative ICU requirement, with a high risk of complications and an incidence of mortality. These patients are quite susceptible to inflammation, dehydration, malnutrition, cardiovascular and respiratory problems, which might develop as a result of fractures as well as surgical stress [2-4, 11]. For these reasons, it is important to consider that postoperative care treatments of geriatric HF patients are a featured issue. Also, the planned follow-up of high-risk geriatric trauma patients in ICU after surgery decreases negative outcomes [4, 6]. In elderly patients, multidisciplinary evaluation of patients and planning of postoperative care treatments are mandatory in the preoperative period to minimize the negative outcomes of HF [4].

There are no clear and objective criteria regarding the decision for the admission of geriatric patients with HF, which is high risk, to ICUs. In addition to many clinical factors that affect the ICU admission, laboratory disorders, such as anemia, hypoalbuminemia, and high urea/creatinine levels also plays role in this decision [5, 12]. As a measure of inflammatory response, elevated CRP and NLR values are also associated with postoperative poor clinical outcomes [13, 14]. However, recent studies argue that preoperative high NLR value can be used as an indicator for high risk of complications and mortality after cardiovascular, oncological surgery, and HF surgery [9, 14-16]. For these reasons, the purpose of the present study was to test our hypothesis that higher NLR value, which was found to be associated with negative outcomes after surgery, may also be associated with admission to

**Table 3.The neutrophil-lymphocyte ratio value of each group (ICU mortality)**

| Group | Median | Interquartile range 25 | Interquartile range 75 | *p* value* |
|---|---|---|---|---|
| Survivor group (n = 168) | 6.42 | 3.55 | 9.44 | **0.015** |
| Non-survivor group (n = 20) | 9.36 | 7.23 | 11.02 | |
| Total (n = 188) | 7.35 | 3.79 | 9.68 | |

*Compared by Mann Whitney U Testi

ICU. As far as we are concerned, the relation of high NLR with postoperative negative results was studied by many studies in the literature [13-16], and its contribution to ICU admission was not investigated adequately.

Biomarkers, such as neutrophil and lymphocyte values, WBC count, acute phase reactants, adhesion molecules, and cytokines are used to determine the inflammatory response in the body. The CBC Test, which is used widely in practice, is very inexpensive and the result is obtained quickly [10, 17]. NLR value is a very simple and easy-to-calculate parameter. Many studies conducted in recent years have shown it to be a parameter determining the degree of stress and inflammation [1, 8-10].

Recent studies have been found in the literature examining the effects of high NLR on postoperative prognosis in various surgical patients [8-10, 13]. Forget *et al*. [8] conducted a study with 82 patients undergoing major abdominal surgery, and found that higher NLR values were associated with postoperative acute complications, but were not associated with CRP, which is an inflammatory parameter. Vaughan-Shaw *et al*. [16] conducted a study with elderly patients who underwent non-traumatic emergency abdominal surgery, and found that higher NLR was associated with increased mortality. Dilektasli *et al*. [15]reported that high NLR value was associated with mortality in 1.356 critical trauma patients in surgical Intensive Care Unit. These studies also show that higher NLR parameter is determined as a prognostic factor in many surgical and trauma patients.

The clinical characteristics of the patients (i.e. advanced age, high preoperative ASA score, comorbid diseases), type and duration of surgery, preoperative duration, anesthesia method, and factors, such as the ICU capacity of the hospital, surgeon and anesthesiology preference also play roles in postoperative ICU and complications [3, 6, 18-21]. Our study was conducted in a restricted geriatric population with ASA 3/4 and with surgical intervention time of < 72 hours, who underwent spinal anesthesia due to femur neck and intertrochanteric fracture. As a reflection of the severity of preoperative comorbidity, the elevated ASA physical condition is one of the most reliable prognostic indices for perioperative mortality, and is also used to predict postoperative complications [3, 6, 18]. In our study; however, no significant differences were detected in inter-group ASA score comparisons. Akbas *et al*. [19] reported that HF patients undergoing general anesthesia over 80 years of age were admitted more to ICU, and mortality was higher in these patients. However, there are also several other studies reporting that the anesthesia method has no effects on admission to the ICU [18, 20]. In our study, homogeneity was ensured in the study population by including only geriatric patients who were operated under spinal anesthesia. Although time to operation was reported as an important risk factor in HF patients for peroperative complications [21], it was found that it did not differ at significant levels between the groups in our study.

Forget *et al*. [8] conducted a study with 237 patients who had HF, and found that the patients had an NLR cut-off value of 4.9 (sensitivity: 62.9%, specificity: 57.6%) for 1 year of mortality after the surgery. Fisher *et al*. [10] conducted a study with 415 patients who had HF, and reported that the elevated NLR (≥ 5.1) value at the time of admission was an important risk factor for postoperative myocardial damage, high inflammatory response/infection, and death in hospital. Temiz *et al*. reported that high NLR values after HA (hemi arthroplasty) were associated with mortality; and the cut-off value was 4.7 in elderly patients [1]. In the same study, the authors also reported that less invasive surgical techniques can be selected elevated NLR values to prevent inflammatory response, as well as using pharmacological agents, such as statins and aspirin to reduce systemic inflammation after surgery [1]. However, these prophylactic treatment recommendations should be examined with extensive clinical trials. Uzbek *et al*. [9] conducted another study with 55 patients who underwent proximal femoral nail surgery alone, and found that the cut-off value of preoperative NLR was 5.25 (sensitivity: 84.6%, specificity: 78.6%); and argued that it was predictive for the risk of postoperative death. In our study, NLR cut-off value (9.65) that was found for admission to ICU was higher than the cut-off values of mortality reported by studies in the literature. However, as far as we are concerned, no other studies were detected in the literature, which were planned with a similar patient population for the admission to ICUs. Similar to our results, Slate *et al*. [22] found that NLR 9.2 cut-off value (HR, 3.60 (1.44-9.18 CI 95%, $p = 0.006$) might be a predictor for 30-day short-term mortality

in acute pulmonary embolism. Similarly, Dilektasli *et al*. [15] reported that an NLR greater than 8.19 was independently associated with in-hospital mortality on the 2nd day of surgery ICU in trauma patients.

When the literature was reviewed, it was found that there were various mechanisms to explain the effect of NLR on the prognosis after orthopedic surgery in the geriatric population [11, 13, 23, 24]. One of them, aging is associated with a high level of proinflammatory cytokines [11]. However, it was also reported that inflammatory markers were independent predictors of postoperative adverse outcomes in elderly trauma patients with reduced physiological reserves [13]. Also, it is considered that the inflammatory response after surgery probably plays roles in organ dysfunction in patients [11, 13, 23]. Lymphocytes are the main components of the humoral and cellular immune system, playing central roles in immune response. Although lymphopenia reflects the weakness of cellular immunity after multitraumas, Neutrophilia can occur due to unbalanced systemic inflammatory response [11, 13, 15]. In addition, previous studies reported that the increase in the neutrophil count in some diseases (e.g. pulmonary embolism, coronary artery disease, deep vein thrombosis) is associated with an increase in thrombus formation [22, 25]. Another mechanism might be the development of the inflammatory response with hormonal changes caused by post-traumatic stress (i.e. increases in serum cortisol levels), which also increases the number of neutrophils, reducing the number of lymphocytes [8, 11, 13, 24]. For these reasons, the inflammatory response that is already increased is expected to increase more with additional surgical trauma. These mechanisms are important in the intensive care management of elderly HF patients, and it is important to identify preventive planning.

### Limitations

The study had some limitations. First of all, it was a retrospective and single-centered study; and therefore, we can only rely on the results of the patients in our center. Secondly, there were many factors that affected patient admission to the Intensive Care Unit. For this reason, the deduction of the causal relation between NLR and the results is limited although we kept the patient population limited.

## CONCLUSION

Despite the limitations of the study, it was concluded that high admission NLR value may be a risk factor for postoperative ICU admission and mortality in elderly patients with hip fractures. NLR can be used as a prognostic parameter in the perioperative management of this critically ill patient population. The repeatability and generalizability of the results must be investigated with multi-centered further clinical trials.

*Authors' Contribution*

Study Conception: ÖHM, OK; Study Design: ÖHM, OK; Supervision: ÖHM, OK; Funding: ÖHM; Materials: ÖHM; Data Collection and/or Processing: ÖHM; Statistical Analysis and/or Data Interpretation: ÖHM; Literature Review: ÖHM; Manuscript Preparation: ÖHM, and Critical Review: ÖHM.

*Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

*Financing*

The authors disclosed that they did not receive any grant during conduction or writing of this study.

*Ethics Committee Approval*

Approval was obtained from the Yozgat Bozok University ethics committee (2019 / 137). Helsinki Declaration guidelines were followed throughout the study.

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The European Research Journal 2021;7(6):635-644 Original Article

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# The impact of weight loss on thyroid autoimmunity - Weight loss decreases thyroid peroxidase antibody levels: a retrospective cohort study

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## ABSTRACT

**Objectives:** Within the last two decades, an increase has been seen both in autoimmune diseases and obesity, therefore, the correlation between obesity and autoimmunity has been questioned and many studies have been conducted on this issue. Based on this relationship, we aimed to determine whether the weight loss affects the thyroid peroxidase (TPO) antibody levels of obese individuals with thyroid autoimmunity or not.

**Methods:** The patients who were aged over 18 years, had a Body Mass Index (BMI) ≥ 30 Kg/m$^2$ and TPO antibody ≥ 5.60 IU/mL were included in the study. The primary endpoint was the change in TPO antibody levels of the patients at the end of the sixth month of the follow-up. The correlations of TPO antibody levels with anthropometric and laboratory measurements were evaluated.

**Results:** At the end of the sixth month of follow-up of the patients, TPO antibody levels decreased after weight loss ($p < 0.001$). No significant correlations were found between the differences in weight, fat mass, muscle mass and TPO antibody levels ($p = 0.171$; $p = 0.656$; $p = 0.939$).

Conclusions: Weight loss caused a decrease in the levels of TPO antibody levels in the obese individuals having thyroid autoimmunity pointing that weight loss might be useful to stop the progression or lead to regression of the disease.

**Keywords:** autoimmunity, autoantibodies, obesity, thyroiditis, thyroid gland, weight loss

Obesity is defined as the accumulation of fat in the body so as to cause illness and is an increasing public health problem since it leads to hypertension, dyslipidemia, cardiovascular diseases, type 2 diabetes and some cancer types [1]. It is known that genetic factors as well as lifestyle and environmental factors play a role in the etiology of obesity. Thyroid autoimmunity is a disease characterized by the formation of special antibodies which target the thyroid gland [2, 3].

Thyroid peroxidase (TPO) is a molecule, which catalyzes very important reactions such as the activation of iodine, iodination of tyrosine residues and coupling of iodinated tyrosine [4]. Thyroid peroxidase antibody positivity is seen in 90% of patients with patients having thyroid autoimmunity and a better correlation has been found between histological findings of thyroiditis and TPO antibody compared to Thyroglobulin (Tg) antibody [5, 6]. Genetic and environmental factors have also been demonstrated in the etiology of thyroid autoimmunity. The environmental factors triggering thyroid autoimmunity include some nutrients (iodine, selenium, vitamin B12, vitamin D

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etc.), pesticides, radiation, some medications (interferonalpha and gamma, Tumor necrosis factor-alpha), pregnancy, infection, stress, smoking and obesity [7].

Within the last two decades, an increase has been seen both in immune-mediated diseases and obesity, especially in the industrialized Western countries [8, 9]. Therefore, the correlation between obesity and autoimmunity has been questioned and many studies have been conducted on this issue [8, 10, 11]. It has been shown that white adipose tissue in obesity is not only an organ where the energy is stored, but also is an endocrine organ, which secretes cytokines that are named adipokines and have proinflammatory activities. It has been demonstrated that cytokines secreted from the white adipose tissue cause inflammation, and especially leptin among adipokines leads to proinflammatory effects by activating T helper (Th1) cells and suppressing T regulatory (Treg) cells. Immune-inflammatory response is exaggerated by increased leptin levels in persons with obesity, causing autoimmune response in people with predisposition. Conversely, decreased leptin levels can cause immune suppression [7, 12, 13]. Therefore, adipokines are thought to play a key role in the interaction between adipose tissue and immune system and in the relationship between obesity, autoimmune and inflammatory diseases [8].

In the result of these studies, the increasing prevalence of obesity and autoimmune diseases has been linked to the relationship between adipokines and the immune system; it has been suggested that complex immunological alterations yield to autoimmune reactions [1, 7, 14]. Based on this relationship, in this study, we aimed to determine whether weight loss of the obese patients with thyroid autoimmunity, who were followed up at an obesity outpatient clinic, caused a difference in the levels of TPO antibodies affecting the course of thyroid autoimmunity.

## METHODS

### Study Design

Data of this retrospective cohort study were obtained from registries of the patients who consecutively admitted to the the Istanbul Medeniyet University, Göztepe Training and Research Hospital, Obesity Outpatient Clinic for the purpose of losing weight between January and July 2016. The primary endpoint was the change in TPO antibody levels of the patients at the end of the 6th month of follow-up.

The study was performed in accordance with the Declaration of Helsinki and was approved by Istanbul Medeniyet University Göztepe Research and Training Hospital Ethical Committee (2019/0187).

### Participants and Data Sources

The inclusion criteria were being aged over 18 years, having a body mass index (BMI) $\geq 30$ kg/m$^2$, a TPO antibody $\geq 5.60$ IU/mL and having thyroid autoimmunity according to their TPO antibody levels. The patients having BMI $< 30$ kg/m$^2$, TPO antibody $< 5.60$ IU/m L and patients on antithyroid drugs were excluded. Age, gender, the drugs used, weight, height, BMI, co-morbid diseases, fat mass, fat-free mass, muscle mass and among the laboratory measurements glucose, Hemoglobin A1c (HbA1c), insulin, Alanine transaminase (ALT), Aspartate transaminase (AST), thyroid-stimulating hormone (TSH), TPO antibody, triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) values were recorded from the files of 260 patients followed-up in the obesity outpatient clinic between January 2016 and July 2016, who met the inclusion criteria. The participants were followed-up every 15 days for the first three months and then monthly with dietary counseling sessions and were prescribed a reduced−calorie and balanced diet (50%-55% of energy as carbohydrate, 30% of energy as fat, and 15%-20% of energy as protein) of self−-prepared foods to achieve weight loss. The correlations of TPO antibody levels with anthropometric and laboratory measurements were evaluated. The weight, BMI, fat mass, fat-free mass, muscle mass and TPO antibody levels of 78 patients who attended visits regularly, lost any amount of weight at the end of the 6th month and whom TPO antibody values were measured (Fig. 1) were recorded from their files. The effect of weight loss on TPO antibody levels was evaluated at the end of the 6th month. Seven of 78 patients were started on levothyroxine therapy during follow-up The levothyroxine doses used were as follows; 4 patients 25 mg, 1 patient 50 mg, 1 patient 75 mg, 1 patient 100 mg levothyroxine.

### Anthropometric Measurements

The height of each patient was measured with a

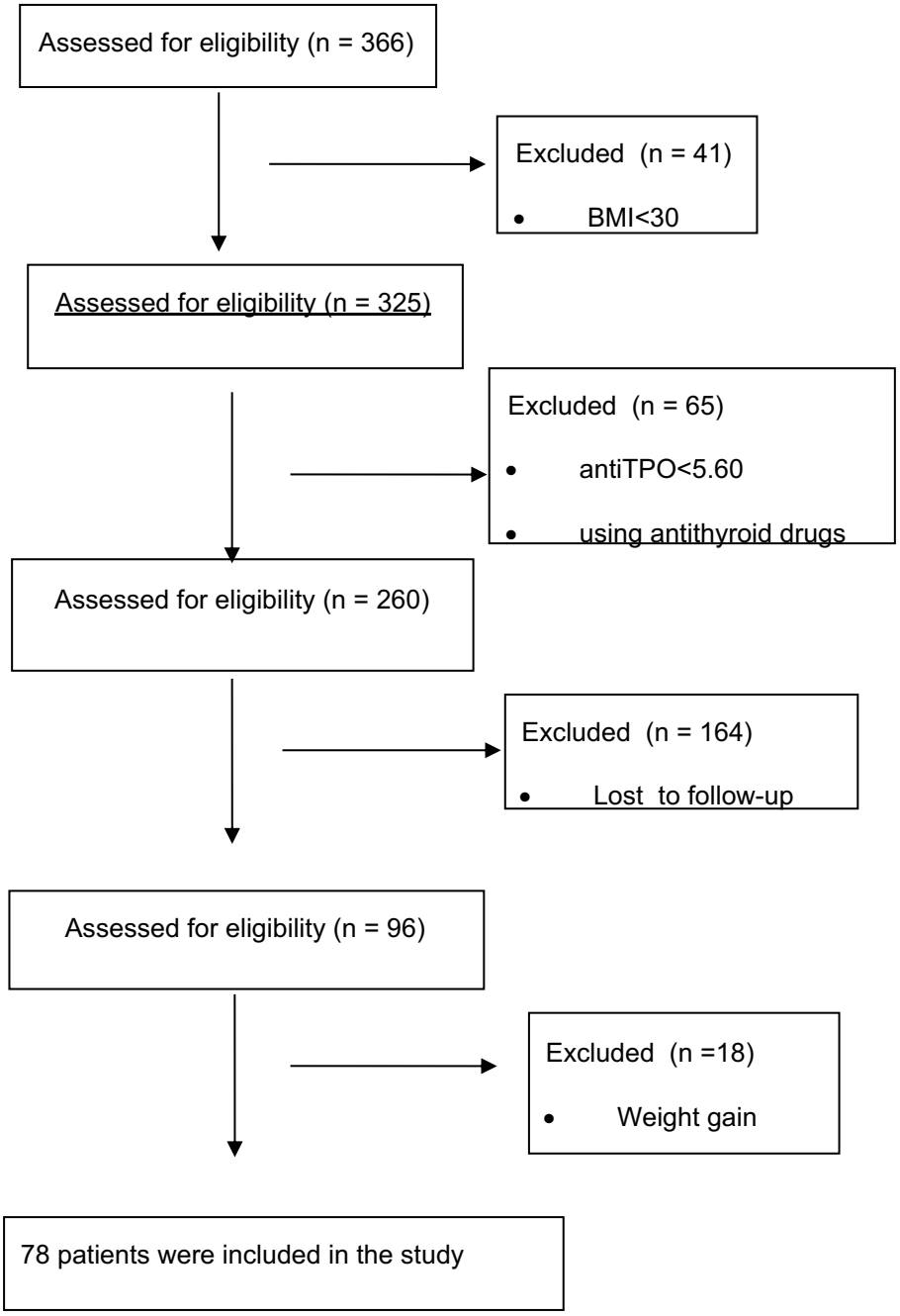


**Fig. 1. Flowchart of inclusion/exclusion of participants.**

stadiometer (SECA) without shoes and as standing. Weight, fat mass, fat-free mass and muscle mass of each patient was measured with bio-impedance analysis device (TANITA MC 780-MA, Tokyo, Japan). BMI was calculated with the quetelete index (kg/m$^2$).

## Laboratory Measurements

Blood samples were collected following a fasting period of 8 to 12 hours. Fasting blood glucose, TG, TC, LDL, HDL, ALT and AST levels were studied with Roche Cobas 8000 analyzer, while insulin was measured with Beckman Gulter Unicel Dx1 800 and HbA1c using Primus MRDV with HPLC technique. Serum reference ranges were accepted as 0.35-4.49 mIU/L for TSH and a cut-off value of 5.60 IU/mL was taken for TPO antibody and these values were determined using the chemiluminescence (ICMA) method with Architect I2000SR. Patients with a TSH between 0.35-4.49 mIU/L were considered to be euthyroid, 4.50-10.0 IU/mL as subclinical thyroid and > 10.0

IU/mL as overt hypothyroid. Patients with an antiTPO ≥ 5.60 IU/mL were accepted to have thyroid autoimmunity.

### Statistical Analysis

Data analyses were performed with the statistical software SPSS for IBM, version 25.0 (SPSS, Inc., Chicago, IL). Normally distributed data were shown as mean ± SD and the data that were not normally distributed were presented as median, minimum and maximum values. Significant differences of normally distributed data were assessed using a t-test and significant difference of not normally distributed data were analyzed using the Mann-Whitney U test. Categorical data were expressed as percentages. Pearson correlation test was applied to test if there is a correlation between weight loss and the decrease in TPO antibodies. A paired two sample test were applied to analyze the effect of weight loss on TPO antibodies. *P* value < 0.05 was statistically significant.

## RESULTS

Baseline characteristics of the initial and final sample included in the study are given in Table 1. Mean age of the participants was 49.23 ± 12.49 years. Because most patients presenting to our obesity clinic were women, 90.8% of the participants were female patients. The mean BMI was found as 37.19 ± 5.19 kg/m2, mean fat mass as 38.21 ± 9.78kg, mean fat free mass as 57.55 ± 8.16 kg and mean muscle mass as 54.23 ± 8.16 kg. Median levels of TPO antibody was found as 169.55 (5.78-1000). The characteristics of the initial and the final sample was similar in terms of age ($p$ = 0,08), gender ($p$ = 0.09), weight ($p$ = 0.64), BMI ($p$ = 0.89), fat mass ($p$ = 0.25), fat free mass ($p$ = 0.56), muscle mass ($p$ = 0.85) and TPO antibody ($p$ = 0.54)

**Table 1. The baseline characteristics of initial and final samples**

| | Initial sample (n = 260) | | Final Sampes (n = 78) | | |
|---|---|---|---|---|---|
| | Mean ± SD | Median (Min-Max) | Mean ± SD | Median (Min-Max) | *p* value |
| **Age (years)** | 49.23 ± 12.49 | 52(18-78) | 51.71 ± 11,26 | 53,5 (23-78) | 0.08 |
| **Gender** | | | | | **0.009** |
| **Female n (%)** | 236 (90,8) | | 76 (96.2) | | |
| **Male n (%)** | 24 (9.2) | | 2 (3.8) | | |
| **Weight (kg)** | 96.26 ± 15.57 | 94.3 (70.4-149.2) | 94.98 ± 15.97 | 92.98 (70.5-45.8) | 0.64 |
| **BMI (kg/m$^2$)** | 37.19 ± 5.19 | 36.4 (30-57) | 37.01 ± 5.92 | 35.7 (30-7) | 0.89 |
| **Fat mass (kg)** | 38.21 ± 9.78 | 37 (22.5-80.3) | 38.75 ± 10.64 | 36.5 (23.1-67.6) | 0.25 |
| **Fat-free mass (kg)** | 57.55±8.16 | 56.25 (37.6-86) | 56.9 ± 8.0 | 54.85 (43.6-81.5) | 0.56 |
| **Muscle mass (kg)** | 54.23 ± 8.16 | 53.1 (27.7-91.8) | 52.98 ± 8.16 | 51.85 (27.7-77.5) | 0.85 |
| **AntiTPO (IU/mL)** | 315.18 ± 343.71 | 169.55 (5.78-1000) | 321.70 ± 346.95 | 202 (5.85-1000) | 0.54 |
| **TG (mg/dl)** | 153.35 ± 84.24 | 136.5 (42-779) | | | |
| **TC (mg/dl)** | 212.03 ± 42.86 | 213 (49-322) | | | |
| **LDL-C (mg/dl)** | 136.12 ± 36.28 | 133 (38-231) | | | |
| **HDL-C (mg/dl)** | 49.1 ± 15.42 | 48 (25-188) | | | |
| **TSH (mIU/l)** | 3.25 ± 4.11 | 2.17 (0.35-39.85) | | | |
| **Glucose (mg/dl)** | 109.95 ± 43.54 | 99 (82-439) | | | |
| **HbA1c (%)** | 6.47 ± 3.86 | 5.8 (4.8-14.6) | | | |
| **Insulin(mIU/l)** | 12,83 ± 6.62 | 11.2 (3-45) | | | |
| **ALT (IU/l)** | 26.15 ± 16.56 | 21 (6-103) | | | |
| **AST (IU/l)** | 21.93 ± 10.05 | 19 (9-70) | | | |

BMI = body mass index, Anti TPO = Thyroid peroxidase antibody, TG = triglyceride, TC = total cholesterol, LDL-C = low density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, TSH = thyroid stimulating hormonel, T4 = thyroxin, HbA1c = glycated hemoglobin, ALT = Alanin transaminase, AST = Aspartat transaminase

(Table 1).

Metabolic syndrome was found in 52.04%, hypertension in 32.7%, diabetes in 15.9%, depression in 9.09%, chronic heart disease in 9.09%, chronic obstructive pulmonary disease (COPD) in 4.1%, and obstructive sleep apnea syndrome (OSAS) in 2% of the participants. 82.6% (n = 226) of the participants were in euthyroid, 12.8% (n = 25) of them were in subclinical hypothyroid and 4.6% (n = 9) of the patients were in an overt hypothyroid state (Table 2).

No significant correlation was found between age, weight, fat mass, fat free mass, muscle mass, and biochemical parameters, and TPO antibody levels of the patients. There was a weak correlation between TPO antibody and BMI values ($p$ = 0.042) (Table 2). The correlation between TPO antibody and BMI values was disappeared after adjusting for age, gender and TSH values ($p$ = 0.094). When the correlation between TPO antibody levels and BMI was analyzed separately, no correlations were detected among the patients in euthyroid, subclinical hypothyroid and overt hypothyroid state (Table 2).

After adjusted for age, smoking, menopause and TSH; no significant correlation was found between TPO antibody and BMI and HbA1c values in female patients ($p$ = 0.84, p = 0.88). When both genders were evaluated and the values were adjusted for age, smoking and TSH values, no significant correlation was found between TPO and BMI and HbA1c values ($p$ = 0.932, $p$ = 0.879).

The characteristics of the final sample including 78 patients at the baseline and 6th month as well as the difference of the characteristics between the baseline and 6th month is shown in Table 3. The median TSH levels of the participants at baseline were 2.37 (0.00-39.85). 78.4% (n = 58) of the participants were in euthyroid, 18.9% (n = 14) of them were in subclinical hypothyroid and 2.7% (n = 2) of the patients were in overt hypothyroid state.

The effect of weight loss on TPO antibody in the final sample that lost weight (n = 78) was the primary endpoint of the study and it was found that TPO anti-

**Table 2. Correlations of baseline TPO antibody levels with anthropometric and biochemical parameters**

| | TPO antibody | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Whole population (n = 260) | | Euthyroid (n = 226) | | Subclinical hypothyroid (n = 25) | | Overt hypothyroid (n = 9) | |
| | r | *p* value | r | *p* value | r | *p* value | r | *p* value |
| **Age (years)** | -.069 | .268 | -.154 | .052 | .304 | .134 | -.013 | .974 |
| **BMI (kg/m$^2$)** | **.126** | **.042** | .037 | .645 | .336 | .100 | .448 | .226 |
| **Weight (kg)** | .042 | .497 | -.037 | .639 | .262 | .206 | .492 | .178 |
| **TC (mg/dl)** | .004 | .950 | .022 | .790 | -.009 | .966 | -.104 | .790 |
| **LDL (mg/dl)** | -.010 | .883 | .012 | .883 | .004 | .984 | -.122 | .755 |
| **HDL (mg/dl)** | .014 | .847 | .085 | .301 | -.242 | .254 | -.509 | .162 |
| **TG (mg/dl)** | .062 | .383 | .038 | .643 | .077 | .726 | **.923** | **0.003** |
| **Fat mass (kg)** | .029 | .675 | -.007 | .928 | .165 | .430 | .106 | .822 |
| **Fat free mass (kg)** | .013 | .855 | -.091 | .259 | .310 | .132 | .571 | .181 |
| **Muscle mass (kg)** | .030 | .666 | -.055 | .488 | .314 | .126 | .395 | .380 |
| **TSH (mIU/l)** | **.169** | **.015** | .142 | .072 | .081 | .700 | -.329 | .388 |
| **Glucose (mg/dl)** | -.004 | .951 | -.103 | .199 | .041 | .846 | .413 | .269 |
| **HbA1c (%)** | -.029 | .680 | -.052 | .518 | .056 | .791 | .446 | .268 |
| **AST (IU/l)** | -.024 | .740 | -.092 | .261 | **.431** | **.040** | .049 | .909 |
| **ALT (IU/l)** | .072 | .312 | .011 | .896 | **.537** | **.007** | .289 | .487 |
| **Insulin (mIU/l)** | .048 | .526 | .016 | .857 | .097 | .692 | .469 | .288 |

BMI = body mass index, TG = triglyceride, TC = total cholesterol, LDL-C = low density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, TSH = thyroid stimulating hormone, T4 = thyroxin, HbA1c = glycated hemoglobin, ALT = Alanin transaminase, AST = Aspartat transaminase, HOMA-IR: Homeostatic Model of Assessment-Insulin Resistance

**Table 3. The characteristics of the 78 patients at baseline and 6 months later**

| | Baseline (n = 78) Median (min-max) | 6th months (n = 78) Median (min-max) | The difference between baseline and 6th month Median (min-max) |
|---|---|---|---|
| **Age (years)** | 53.00 (21.00-78.00) | 53.00 (21.00-78.00) | |
| **Weight (kg)** | 96.95 (71.10-134.60) | 90.70 (67.00-117.90) | -5.95 (-22.3—0.80) |
| **BMI (kg/m²)** | 35.95 (31.20-50.00) | 34.40 (28.10-42.30) | -2.00 (-8.2-0.10) |
| **Fat mass (kg)** | 40.35 (23.10-60.20) | 36.55 (20.90-50.90) | -3.50 (-12.50-0.90) |
| **Fat-free mass (kg)** | 55.55 (47.40-81.50) | 55.65 (45.30-78.70) | -1.30 (-4.20-2.20) |
| **Muscle mass (kg)** | 52.00 (27.70-77.50) | 51.75 (28.60-74.80) | -1.20 (-4.00-2.10) |
| **TPOAb (IU/mL)** | 111.61 (7.92-1000) | 84.5 (0.50-1000) | -25.41 (-283.74-5.45) |
| **TSH (mIU/l)** | 2.37 (0.00-39.85) | - | |

BMI = body mass index; TPO Ab =: Thyroid peroxidase antibody, TSH = thyroid stimulating hormone

body values decreased after weight loss ($p < 0.001$) (Fig. 2). When the effect of weight loss on TPO antibody in euthyroid, subclinical hypothyroid and overt hypothyroid groups were analyzed separately, the effect of weight loss was more evident in the euthyroid group than the hypothyroid group. The effect of weight loss wasn't observed in the overt hypothyroid group, however the number of the patients in this group was too small (n = 2) (Fig. 3).

The correlation between weight difference and TPO antibody difference was also investigated in the study. Weight and TPO antibody difference were calculated by subtracting the weight and TPO antibody values obtained in the second visit from the first visit. Visually such correlation can be seen from a scatter plot as depicted in Fig. 4. Fig. 3 implies that there is not relationship between difference in weight and difference in TPO antibody levels (r = 0.167, $p = 0.171$). Likewise, no significant correlation was found between the differences in fat mass and TPO antibody (r = 0.067, $p = 0.656$) (Fig. 5) and the muscle mass and TPO antibody values (r = -0.011, $p = 0.939$) at the end of the 6th month.

In our laboratory, antibody titers above 1000 IU/ml could not be calculated and were reported as > 1000 IU/ml. The values reported as > 1000 IU/ml were analyzed as 1000 IU/ml (n = 32). Therefore, the difference in TPO antibody values did not reflect the actual difference. This was the most important limitation of our study.

## DISCUSSION

In this study it was observed that TPO antibody levels decreased after weight loss at the end of the 6th

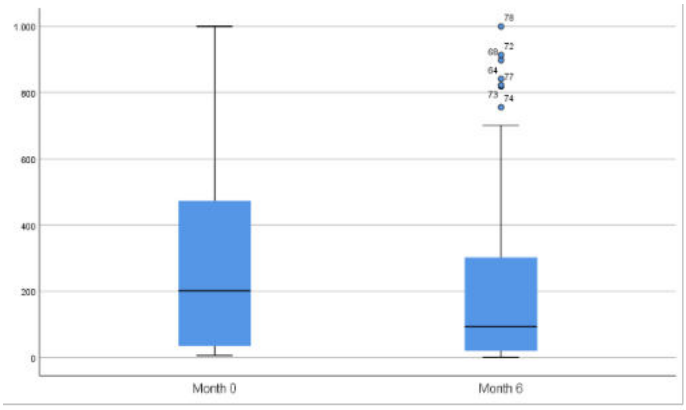


**Fig. 2. The effect of weight loss on TPO antibody.**

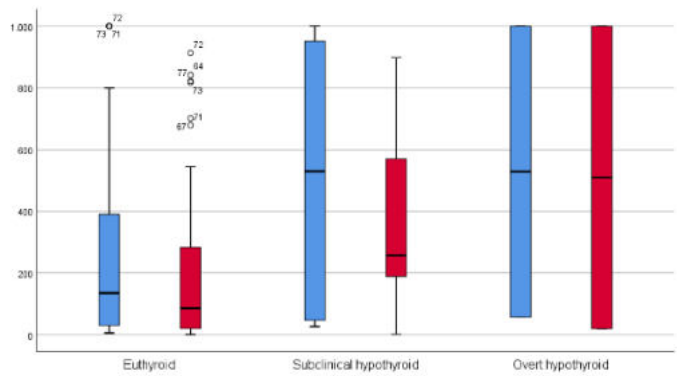


**Fig. 3. The effect of weight loss on TPO antibody in euthyroid, subclinical hypothyroid and overt hypothyroid group.**

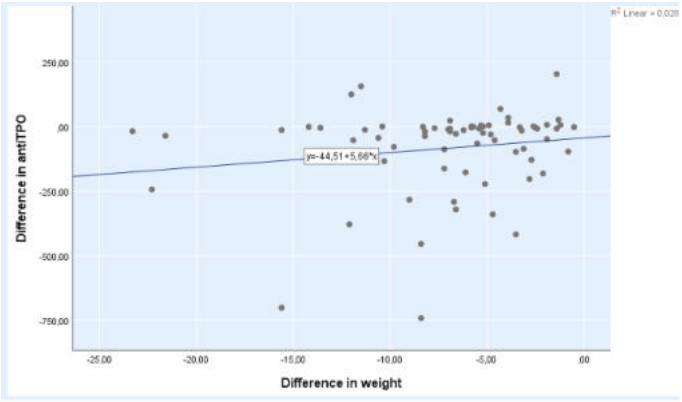


**Fig. 4. The correlation between difference in weight and TPOAb difference in the 6th month.**

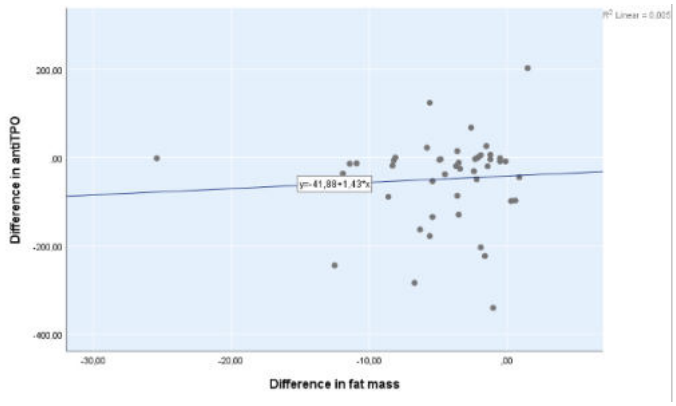


**Fig. 5. Correlation between difference in fat mass and TPOAb in the 6th month.**

month of follow-up and the effect of weight loss was more evident in the euthyroid group.

It has been demonstrated in a study that TPO antibody titers histopathologically show the degree of thyroid inflammation [6, 15]. In a study conducted by dividing euthyroid persons into two groups according to the presence of TPO antibody, higher TSH levels were shown in persons with a positive TPO antibody titer [7]. In a study including subclinical hypothyroidism, overt hypothyroidism and control groups; there was no significant difference between subclinical and overt hypothyroidism groups in terms of TPO antibody levels, while the lowest value was found in the control group [5]. In our study, TPO antibody levels were significantly higher in patients with overt hypothyroidism compared to those with subclinical hypothyroidism and in patients with subclinical hypothyroidism compared to the controls. There was a significant positive correlation between TPO antibody and TSH levels. Our findings supported the literature.

There are studies showing that the risk of thyroid autoimmunity is higher in persons with obesity and that being overweight in childhood increases the risk of development of thyroid autoimmunity between 60-64 years of age [16]. In addition, it was observed that thyroiditis is exaggerated as the level of obesity increases in patients with thyroid autoimmunity [17]. Studies investigating the relationship between BMI and TPO antibodies have reported different results. In the Danish National Birth Cohort study examining the correlation between BMI and the risk for development of autoimmune diseases; linear correlations were demonstrated between BMI and development of all autoimmune diseases except for ankylosing spondylitis, inflammatory bowel disease and sarcoidosis [14]. In a study from China, BMI was found to be correlated with TPO antibodies in women, while this correlation was not present in men. It has been reported that gender affects the correlation between obesity and autoimmune thyroiditis. This was thought to have resulted from the differences between women and men in terms of the distribution of body fat and secretion of adipokines and from the higher immune response in women [18, 19]. Unlike these studies, Knudsen *et al*. [20] could not detect a significant correlation between BMI and TPO antibody. In our study, there was a significant weak correlation between BMI and TPO antibody in patients with thyroid autoimmunity, but the significance was disappeared when the effect of TSH was considered.

In a study by Chen *et al*. [20], when adjusted for age, smoking, TSH, and menopause only in female patients, TPO antibody positivity was correlated with BMI, HbA1c, HDL, LDL, TC, TG, fasting plasma glucose (FPG) and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). The same correlation was not found when considering both genders and only male patients [20]. In our study, 91% of all participants were female and similarly to the above-mentioned study, no correlation was found between TPO antibody and these parameters when only female patients were considered. Again, no significant correlation was found between TPO antibody and these parameters when both genders were analyzed.

Studies have shown that obesity predisposes to many autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, psoriasis, type 1 DM, inflam-

matory bowel disease and autoimmune thyroiditis and increased severity of these diseases [8, 10, 21]. On the other hand, studies about the effect of weight loss on autoimmune diseases are limited. In a review of many clinical trials, it was reported that psoriasis symptoms decreased in patients who lost weight and weight loss facilitated the treatment in these patients [22]. In a study conducted in patients with obesity with rheumatoid arthritis, a correlation was reported between BMI and number of the joints with arthritis and severity of the disease, and improvement in body composition should be a part of rheumatoid arthritis treatment [23]. Previous studies have only investigated the relationship between change of thyroid hormone levels with respect to body weight, ignoring the levels of TPO antibodies [24]. We could not find any study conducted about investigating the relationship between weight loss and TPO antibodies levels in thyroid autoimmunity in the literature. We consider this is the first study about this topic.

In a study searching the relationship between low-carbohydrate diet and thyroid autoimmunity, one group was given a diet rich in vegetables, protein, milk and dairy products, and poor in carbohydrates and the other group was given a reduced-calorie diet. In the carbohydrate-poor diet group a significant decrease in TPO antibodies was observed, while no change was detected in the reduced calorie diet group. However, those who were on a diet poor in carbohydrates had more weight loss. In our study, although the participants did not obey the same diet, weight loss led to decrease in TPO antibodies particularly in patients with euthyroid state [25].

Besides cytokines that have proinflammatory effect, adipokines which have anti-inflammatory effects are also secreted by the adipose tissue. Studies have shown that leptin which has proinflammatory effect was decreased and adipokines that have anti-inflammatory effects were increased in patients who lost weight after bariatric surgery [26-28] Other studies have reported that excessive inflammatory activity was decreased and anti-inflammatory activity was increased in persons who lost weight with diet and increased physical activity [26, 29]. In a study on mice, it was found that first immune response was increased with weight loss and then the immune response was decreased as weight loss was continued [30]. In a genetical study, it was shown that inflammation related gene expression in adipocytes and macrophages were modified and inflammatory response was decreased with weight loss [31]. This could explain our result as weight loss suppresses inflammation, and thus excessive immune response occurring against this, and accordingly provides a decrease in TPO antibodies.

In a study that compared the patients with and without obesity, weight loss was shown to decrease immune response in both groups, and this decrease was similar in these two groups [32]. In our study, all participants were affected with obesity, and therefore we could not perform this comparison, but we found that weight loss decreased TPO antibodies in persons with obesity and attributed this to the decreased immune response in these persons. On the other hand, to link the decrease in serum TPO antibody levels for six months, relatively a short observation period, to the reduced immune response, further controlled and long-term studies are needed.

### Limitations

This study has several limitations. First, the number of participants was relatively small, and a large part of the participants lost from the follow up. However, due to the duration of the study, the high drop-out is expected, especially in a study examining an obesity outpatient clinic. Second, antibody titers above 1000 IU/ml could not be calculated in our laboratory and reported as >1000 IU/ml (n = 32). Therefore, difference in the TPO antibody levels could not be calculated in an accurately. Third, the study was conducted retrospectively and as a result it was not possible to take a control group. Forth, since this was a retrospective study the patients who had TPO antibody levels at baseline and 6th month were included in the study. The baseline TSH values were recorded from the patient's files however most of the patients' TSH levels could not be obtained from their files because TSH values of the patients were checked at various times other than the 6$^{th}$ month. Last, hence, mostly women refer to our obesity outpatient clinic, a high female/male ratio was detected in the study.

## CONCLUSION

Today, the reason for the increase in autoimmune diseases is an issue of concern. Many factors have

been held responsible for this increase. Many studies have shown obesity as the most important factor for this increase. In our study, weight loss was found to decrease TPO antibody levels in persons with thyroid autıimmunity. We attributed this to decreased autoimmunity by weight loss in thyroid autıimmunity. However, further comprehensive and randomized-controlled studies are needed to confirm this.

*Authors' Contribution*

Study Conception: HHM, HHM; Study Design: HHM, HHM; Supervision: HHM, HHM; Funding: HHM; Materials: HHM; Data Collection and/or Processing: HHM, HHM; Statistical Analysis and/or Data Interpretation: HHM, HHM; Literature Review: HHM, HHM; Manuscript Preparation: HHM, HHM and Critical Review: HHM, HHM.

*Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

*Financing*

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# Preferences of speech and language therapists for telepractice in the COVID-19 pandemic and factors affecting their acceptance of the delivery model

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## ABSTRACT

**Objectives:** With the COVID-19 pandemic, telepractice became a great option in speech-language therapy services, as in many healthcare utilities. However, the transition to this service model did not occur at a similar rate for every clinician. Therefore, this study aimed to determine the experiences, preferences and factors affecting the acceptance of speech-language therapists (SLT) regarding telepractice in Turkey.

**Methods:** Sixty-seven SLTs were presented with a questionnaire that addressed the professional tendencies, experiences and views on telepractice of them. Descriptive statistics regarding the preferences and experiences of SLTs were calculated. Moreover, factors that might be related to the number of sessions they held at the pandemic were examined with the Chi-squared test.

**Results:** The speech-language disorders that SLTs find the most suitable for telepractice were fluency disorders, voice disorders and speech sound disorders. Groups that SLTs deemed most suitable for receiving telepractice in terms of age were 12-21, 22-64 and 7-11, respectively. A significant relationship was found between the frequency of online meetings and telepractice sessions before the pandemic and the number of sessions during the pandemic. Furthermore, a significant relationship also was found between satisfaction with using clinician skills in telepractice and the number of telepractice sessions during the pandemic.

**Conclusions:** The importance of the first experiences of SLTs in the acceptance of the delivery method emerged. The necessity of in-service trainings and exemplary models to improve attitudes emerged. With these trainings, ensuring security, standardizing practices and increasing qualified services will be provided as well.

**Keywords:** Telepractice, speech and language therapy, COVID-19 pandemic, technology acceptance, clinicians' perspective

After COVID-19 was first identified in Wuhan province of China, it spread all over the world at an unexpected speed. Thus, this process caused a great change in the daily lives of individuals in Turkey as well as in the world, and deeply affected their access to services such as education and health [1, 2].

One of the professional professions that provide services in the field of health is speech and language therapy (SLT). Clinicians in this field actively serve in the evaluation and therapy of communication, lan-

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guage, speech, voice and swallowing disorders in the clinical field [3]. Before the pandemic, these services were widely offered in-person in clinics, rehabilitation centers or hospitals [4]. However, SLTs work in in-person sessions in environments with high risk of transmission of the virus due to services that require close contact like many healthcare professionals. For this reason, as recommended by the American Speech and Language Association (ASHA) [5] and the Association of Speech and Language Therapists (DKTD) in Turkish [3], in-person services were decommissioned in Turkey as a precaution against the risk of those clinicians getting infected. In this context, the search for alternative services increased in order to maintain the therapy service.

An important alternative to in-person services is telepractice (i.e. telehealth, telemedicine and telerehabilitation). This service model is the usage of telecommunication technologies for evaluation and therapy between clinician and client, and for consultation between clinicians [6]. There is evidence that this model can be suitable and effective in many disorders. Voice disorders [7], dysphagia [8], stuttering [9], aphasia [10], communication, speech and language impairments due to the autism spectrum disorder [11], and speech sound disorders [12] can be shown as examples to these disorders.

Telepractice is seen as an alternative service option with many advantages [13]. In some clients, telepractice may be the main way for clients to reach services, just as in the circumstances of the COVID-19 pandemic [5]. In many studies, it is emphasized that the main advantage of telepractice is access to services and flexibility of time and place. Other advantages are reported as cost efficiency and user satisfaction [13-17]. However, there are also many limitations regarding telepractice. Some examples that can be given to this situation are that the application protocols are not clear yet, problems in material selection, technological problems, uncertainty in cost-benefit analysis, unclear candidate criteria and difficulties in ensuring active participation of the client over the Internet [18-20]. Studies examining the experience of clinicians regarding telepractice services have an important place in the literature of SLT. Wales *et al*. [21] reviewed studies on access to SLT services through telepractice in primary school children. The authors reported that there was some promising evidence that telepractice could be used in this group. Weidner and Lowman [22] reviewed the role of some factors in telepractice services for adults. The main categories were issues such as client types, intervention approaches, and technology. The authors reported that there was evidence for the usage of telepractice in the management of many diseases such as aphasia, dysphagia and Parkinson's disease. Group therapies are also preferred in some studies. The authors also reported that teleconferencing systems such as Zoom and Adobe Connect are preferred in telepractice.

As in any new technology, determining the factors that make clinicians and clients accept this model is seen as an important issue regarding telepractice. For example, some socio-demographic characteristics such as education level, culture, age or gender were found to be effective in technology acceptance [22, 23]. As another example, Tucker [24] concluded that telepractice is mostly preferred by young SLTs. The fact that they are more competent and willing to use technology was stated as the reason for this. Another remarkable point in this context is the experience in technology according to Sun and Zhang [25] and Tucker [18]. Individuals who spend more time with these technologies have higher levels of acceptance. Technology acceptance levels were also discussed in some models. For example, Dunkley *et al*. [26] discussed their telepractice experiences in SLT within the scope of the Technology Acceptance Model [27]. In this model, the two most critical components in the acceptance of technology are specified as "perceived ease of usage" and "perceived usefulness" regarding the technology in question. Dunkley *et al*. [26] also reached conclusions supporting this model.

There are also various barriers and concerns about providing telepractice services. One of the most important concerns about telepractice is related to the level of the therapeutic relationship established with the client. However, the first evidence is that there is not a great deficiency in telepractice in this regard [28, 29]. Moreover, there were many suggestions on how to improve the relationship in telepractice. For instance, in one study, SLTs emphasized the importance of staying in touch with families and sharing phone or e-mail information [29]. Another concern is that service delivery with telepractice will have a negative im-

pact on the therapy process and clinician skills. However, it is argued that this barrier will decrease as technology develops [30, 18].

In Turkey, there is only one work containing the mixed-study method on telepractice in the SLT field [4]. In this study, the effectiveness of stuttering therapy through telepractice in adults and the participatory and clinician perspectives on this service were examined. Consequently, evidence was obtained that telepractice could be as effective as in-person therapy in adult stuttering and that this delivery method might be suitable for stuttering therapy.

### Purpose

The purpose of this study was to examine the preferences and acceptance processes of SLTs who use telepractice, such as client groups, session duration or software used during the COVID-19 process. In line with the telepractice literature, some study questions and hypotheses regarding possible relationships between these variables were defined:

*1. Does the number of telepractice sessions that SLTs do after the pandemic change according to their 'demographic characteristics'?*

According to the hypothesis determined regarding this study question, the number of telepractice sessions performed after the pandemic does not change according to demographic characteristics (H0). In this decision, it was effective that the ratio of women to men was not balanced among the participants and that the working group was mostly composed of young participants.

*2. Does the number of telepractice sessions performed by SLTs after the pandemic change according to their "online meeting and telepractice experience" and "computer use skills they perceive about themselves"?*

According to the hypothesis related to the second study question, it is expected that the number of telepractice sessions performed by SLTs after the pandemic will change according to their "online meeting and telepractice experience" and "computer use skills they perceive about themselves (H1).

*3. Do SLTs' satisfaction levels in telepractice-related issues (development of the client, therapeutic communication, ability to use clinician skills, software used and financial gain) vary according to the number of telepractice sessions they have held in the last month?*

In the hypothesis related to the third study question, a higher level of satisfaction with this service delivery model of SLTs who perform a higher number of telepractice sessions after the pandemic is expected (H1).

In this pandemic period which significantly affected the level of SLT service, exposing the factors that affect acceptance levels for the SLT telepractice in Turkey is expected to contribute to the development and future maintenance of these services. Moreover, the groups to which the SLTs will provide with this service, the time they schedule, the approaches they prefer, their orientation to use software or hardware will provide an "initial guide" for clinicians who want to provide telepractice services.

## METHODS

### Participants

The participant group of the study consisted of 67 SLTs between the ages of 22-47. The average age of the participants was 29.57 ± 6.78 years. The basic criteria for the inclusion of SLTs in the study were determined as "to have at least a bachelor's degree in the field of SLT" and "to apply at least one session of telepractice". Participants were selected using the appropriate sampling method [31]. While 51 of the participants were women, 16 of them were men. Furthermore, 32 of this group were undergraduate, 34 had a master's degree and 1 was a doctoral graduate.

### Research Ethics

The approval of the ethics committee of the study was obtained from Üsküdar University, Non-Interventional Research Evaluation Board (Number: 61351342 / 2020-244). The study was conducted in accordance with the Declaration of Helsinki.

### Data Collection Tools

In order to collect the data, the questionnaire called “The Experiences of Speech and Language Therapists Regarding Telepractice Services in the COVID-19 Pandemic” was used. In the process of developing the questionnaire, the telepractice literature

[16, 18, 19, 24] and guidelines on the maintenance of SLT services in the COVID-19 pandemic published by ASHA [5] and DKTD (ASLT) [3] were reviewed. Afterwards, related topics were discussed by the authors and various themes were determined. After the questionnaire items were written, clinician opinions were received from three experienced academicians. Finally, a pilot study was conducted with three experienced clinicians and the questionnaire was finalized in line with the feedback received.

The questionnaire consisted of four sub-dimensions which were demographic and occupational information, overview, disorders and satisfaction: (1) Within the scope of demographic information, there were multiple-choice questions and question that they could choose more than one answer about the age, gender, professional experience, and types of clients they worked with. (2) In the overview section, there were multiple choice questions that evaluate the general view of SLTs regarding telepractice. (3) In the disorders section, questions about the suitability of speech and language disorders to telepractice were included with scoring based on five-point Likert grading. (4) In the satisfaction section, there was a five-point Likert scale in which SLTs scored their satisfaction levels in various subjects from telepractice.

## Procedure

The survey was uploaded to Google Surveys and the link of the survey was shared in professional e-mail groups and social media accounts. When the targeted number of participants was reached, the questionnaire was closed to answer.

A directive was presented to the participants at the beginning of the survey. In the directive, information was given on the purpose of the questionnaire, participant criteria, and average response time and data confidentiality. No negative feedback was received from the participants that required correction.

## Statistical Analysis

Descriptive statistics such as frequency, percentage and ratio were calculated in the analysis of the data. Participants' age, gender, perceived computer use skills, online meeting and telepractice experience before COVID-19, and the number of therapies and satisfaction levels of the COVID-19 pandemic were compared with the Chi-square test.

# RESULTS

In this study, in which SLTs' preferences for telepractice services and their experiences regarding acceptance processes in the COVID-19 pandemic were examined, four sub-dimensions addressing the demographic and professional information of SLTs', their general view of telepractice, the disorders in which telepractice was deemed appropriate and their satisfaction level with telepractice were evaluated.

### *Findings on demographic and professional characteristics of the participants*

Findings regarding the demographic information and professional characteristics of the participants were presented in Table 1.

### *At what level did SLTs see their computer skills?*

SLTs often saw their computer use skills as normal or better. The most preferred option was 'good' level (n = 37). The number of SLTs (n = 15) using comput-

**Table 1. Findings on demographic and professional characteristics of the participants**

| Variable | n = 67 | % |
|---|---|---|
| **Gender** | | |
| Woman | 51 | 76.1 |
| Man | 16 | 23.9 |
| **Professional experience** | | |
| 1-2 years | 31 | 46.3 |
| 3-5 years | 14 | 20.9 |
| 6-10 years | 12 | 17.9 |
| 11-15 years | 7 | 10.4 |
| +16 years | 3 | 4.5 |
| **Institutions Served[1]** | | |
| Private education and rehabilitation center | 40 | |
| Speech and language therapy clinics | 37 | |
| Private hospital | 7 | |
| Public hospital | 1 | |
| University | 7 | |
| Other | 3 | |

[1]Due to the fact that many SLTs served in more than one type of institution, the total number of frequencies in the category of institutions served was higher than N = 67.

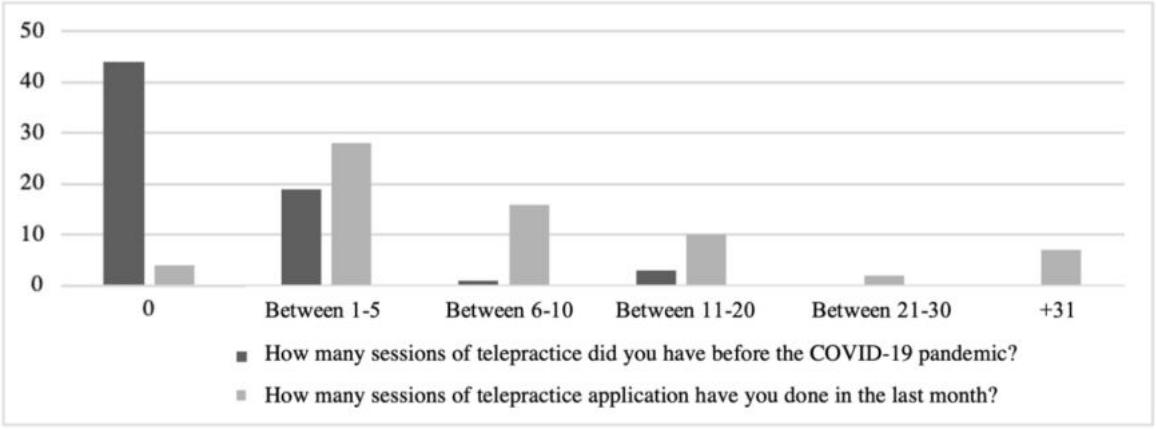


**Fig. 1. Number of telepractice sessions before and after the COVID-19 pandemic.**

ers at 'normal' (n = 15) and 'very good' (n = 14) level was almost equal.

*How often did SLTs have online meetings before the COVID-19 pandemic?*

According to the findings regarding the frequency of SLTs having online meetings before the COVID-19 pandemic, almost half of the participants reported that they had 'never' online meetings (n = 33). 24 SLTs stated that they had 'almost never' online meetings and 10 SLTs stated that they had online meetings 'sometimes'.

*How many telepractice sessions did SLTs have before and after the COVID-19 pandemic?*

The comparative number of telepractice sessions performed by SLTs before and after the COVID-19 pandemic (in the last month) was given in Fig. 1. It was observed that almost half of the SLTs did not apply any telepractice sessions before the pandemic (n = 44). The number of SLTs applying 1-5 sessions was only 19. After the pandemic, 28 SLTs performed between 1-5, 16 SLTs between 6-10 and 10 SLTs 11-20 sessions. Four SLTs reported that they never performed telepractice after the pandemic.

*What were the experiences and thoughts of SLTs about group telepractice?*

According to the answers given by the participants to the questionnaire regarding group therapy applications, 65 SLTs stated that they had not used group therapy in telepractice applications before. SLTs preferred the most partially appropriate (n = 20) and absolutely appropriate (n = 15) options regarding the application of group therapy in telepractice.

*Which technological problems were encountered most frequently in telepractice?*

According to the responses of the participants to the questionnaire regarding whether they had any problems during telepractice, it was observed that 46 SLTs experienced various problems during telepractice, and 21 SLTs did not have any problems. Considering the distribution of the problems faced by SLTs who reported having problems, internet disconnections (n = 31), sound problems (n = 30) and visual problems (n = 29) were experienced most commonly. The least problematic issues were reported as software-related problems (n = 8), computer-related problems (n = 9) and other (n = 2) problems.

*Which teleconferencing softwares were used most frequently in telepractice?*

Considering the distribution of software preferred by the participants during telepractice applications, it was seen that the majority of them conducted their telepractice sessions via the Zoom (n = 53) application. The two most frequently used softwares following it were Whatsapp (Video Call) (n = 30) and Skype (n = 24). The frequency of the usage of FaceTime, Adobe Connect and other software was equal (n = 3). None of the participants reported that they used Webex and Discord programs.

*How many minutes were the telepractice session duration determined?*

Almost half of the SLTs (n = 35) reported that they generally determined the telepractice sessions as 30 minutes. The other SLTs stated that they had longer telepractice sessions of 40 minutes (n = 26), 45 min-

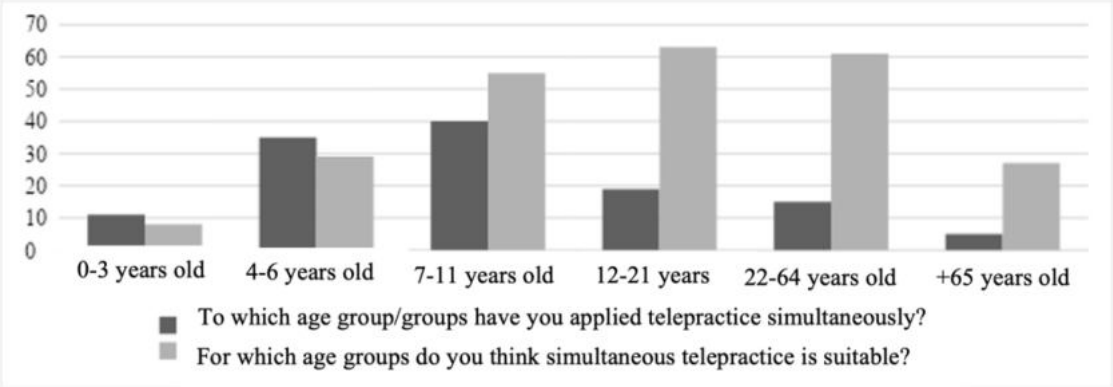


**Fig. 2. Age groups applied and appropriate for telepractice session.**

utes (n = 22) and 60 minutes (n = 11). One participant marked the "other" option.

*What were the age groups in which SLTs most frequently applied and deemed suitable for telepractice?*

The age groups in which SLTs practiced telepractice and that they thought suitable for telepractice were given in Fig. 2 comparatively. The main age groups that SLTs found most suitable for telepractice were 12-21 (n = 63), 22-64 (n = 61) and 7-11 (n = 55). However, when looking at clinical applications, there was a situation that was not consistent with the age ranges found appropriate. Because, SLTs did the most telepractice sessions with children aged 7-11 (n = 40) and 4-6 (n = 35), respectively.

*In which client groups were helpful support needed?*

The distribution of the client groups that the participants worked and needed assistant support during their telepractice applications was given in Figure 3. As seen in Fig. 3, 66 SLTs preferred to work with SSD in telepractice, 64 SLTs delayed speech and language (DSL) and 58 SLTs stuttering and other fluency disorders. Among these client groups studied, those that most require helpful support were SSD (n = 41), DSL (n = 34), developmental communication disorders such as autism, etc.

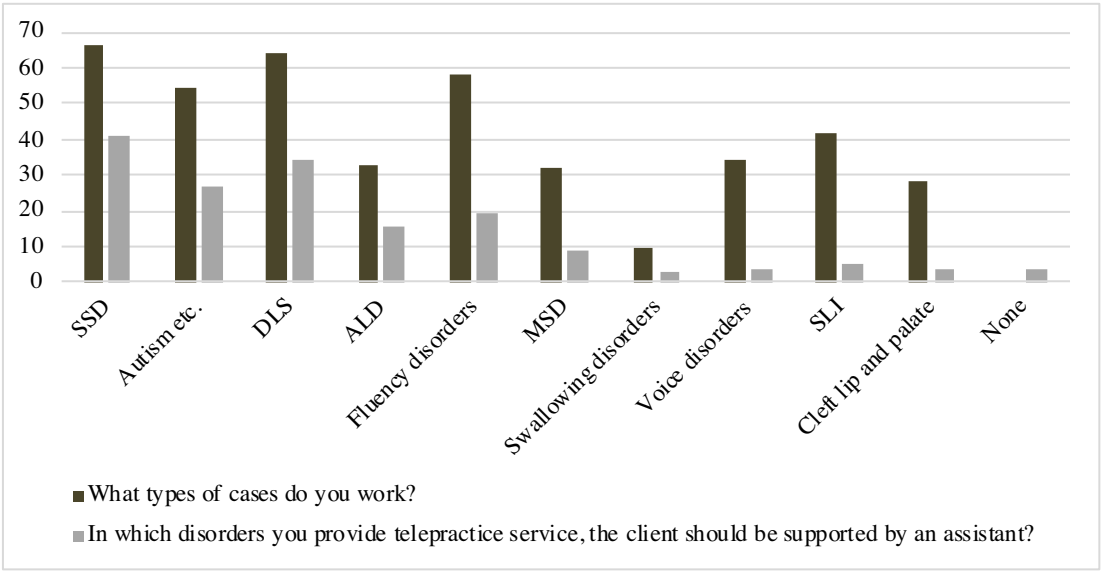


**Fig. 3. Client groups that participants worked and required assistant support during telepractice. SSD = Speech Sound Disorders, DSL = Delayed Speech and Language, ALD = Acquired Language Disorders, MSD = Motor Speech Disorders, SLI = Specific Language Impairment, CLP = Cleft Lip and Palate.**

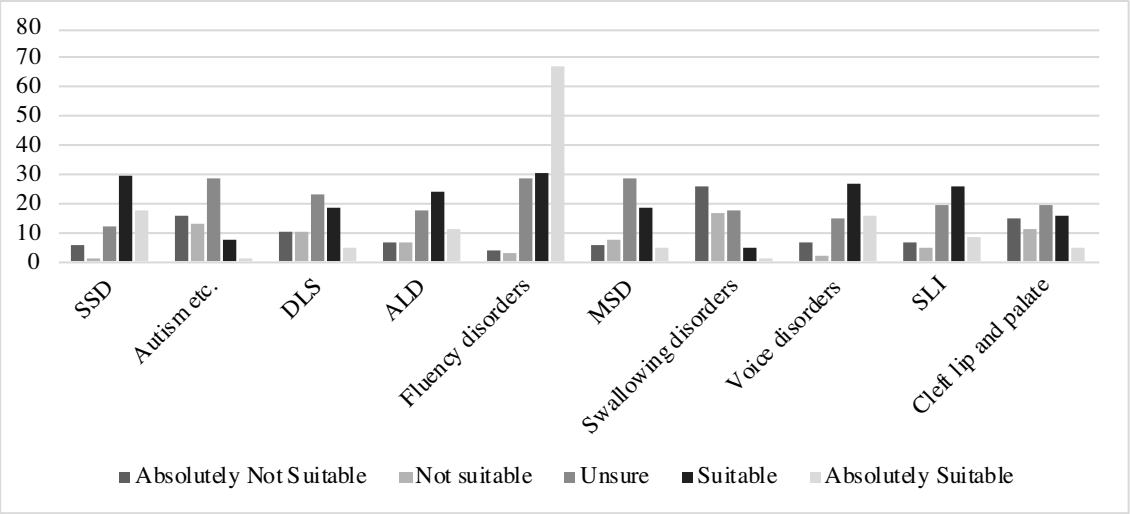


**Fig. 4. Client groups that participants deem suitable for telepractice applications. SSD = Speech Sound Disorders, DSL = Delayed Speech and Language, ALD = Acquired Language Disorders, MSD = Motor Speech Disorders, SLI = Specific Language Impairment, CLP = Cleft Lip and Palate.**

*Which client groups was telepractice suitable for?*

As shown in Figure 4, the main disorders that SLTs most frequently marked the 'absolutely appropriate' options were fluency disorders (n = 31), voice disorders (n = 16) and SSD (n = 18), respectively. The 'suitable' option was most frequently marked in speech and voice disorders (n = 30), fluency disorders (n = 29), voice disorders (n = 27) and specific language impairment (n = 26). The disorder that was considered to be absolutely unsuitable for telepractice was swallowing disorder (n = 26).

*What were the satisfaction levels of SLTs in different subjects related to telepractice?*

In the last part of the questionnaire, five questions were asked to evaluate the satisfaction of SLTs regarding telepractice. As can be seen in Fig. 5, the highest satisfaction level was related to the software used in telepractice (n = 26) and the lowest level of satisfaction was related to the financial gain provided by telepractice (n = 10). Most of the SLTs stated that they were partially satisfied with the level of using the clinician skills (n = 24), the development of the clients (n = 25) and the financial gain (n = 24) in the telepractice process.

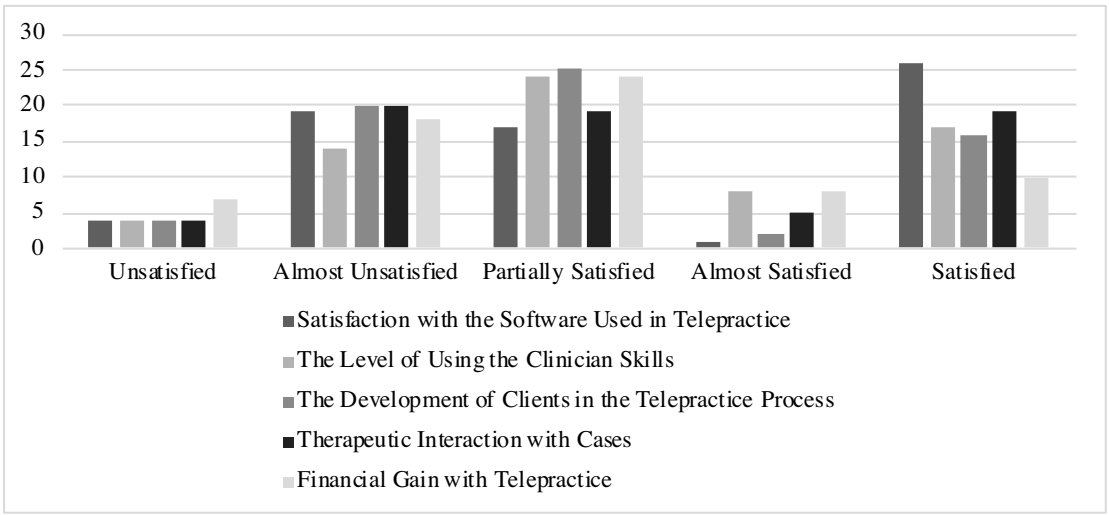


**Fig. 5. Distribution of participants' satisfaction with telepractice according to different subjects**

*Findings on the relationships between the telepractice sessions of SLTs after the COVID-19 pandemic and some variables*

According to the first findings of the study, there was no relationship between 'gender' and 'perceived computer use skill' and 'the number of therapies they performed during the pandemic period' in SLTs (relatively; x2 = 6.635, $p = 0.203$; x2 = 13.592, $p = 0.734$).

There was a significant correlation between 'the frequency of online meetings conducted by SLTs before the pandemic' and 'the number of sessions they had during the pandemic period' (x2 = 19.028; p = 0.012). There was a significant relationship between 'the telepractice sessions SLTs did before the pandemic' and 'the number of telepractice sessions they performed during the pandemic period' (x2 = 25.459; $p = 0.013$).

There is no significant relationship between 'the number of sessions' of SLTs in the last month and satisfaction from 'software used', 'development of clients', 'therapeutic communication' and 'financial gain' (relatively; x2 = 18.991, $p = 0.640$; x2 = 22.140, $p = 0.225$; x2 = 21.509, $p = 0.216$; x2 = 21.011, $p = 0.229$). Only a significant relationship was found between "satisfaction with the level of using clinician skills" and "the number of sessions they had in the last month" of SLTs (x2 = 25.903; $p = 0.048$).

## DISCUSSION

In this study, the factors affecting the preferences and acceptance processes of language and speech therapists for telepractice in the COVID-19 pandemic were examined. As a result of the study, various findings were obtained regarding the demographic and professional information of the speech and language therapists, their general view on telepractice, the disorders they deem appropriate for telepractice, and their level of satisfaction with telepractice.

In this study, it was seen that the first two prominent findings were related to the familiarity and experience with telepractice. SLTs, who had pre-pandemic experience in the use of teleconferencing platforms socially or professionally, easily adapted to provide telepractice services under pandemic conditions. It was previously stated that experience with these technologies has a determining role in attitudes towards future use [4, 30, 32]. The effect of initial experiences on attitudes and preferences was also reported in studies in other health areas [33-36]. At this point, in the light of the studies on the subject, the importance of SLTs following the model telepractice sessions and of encouraging them for first trials emerged [34].

Another important finding of the study was that there was a significant relationship between "satisfaction of using clinician skills" and "the number of sessions they did in the last month" of SLTs in an online environment. It was stated by some authors that telepractice might have a negative effect on clinician skills [30, 24, 37]. Although there was no relationship between "satisfaction with the development of the clients" and "the number of sessions they held in the last month", this finding could be considered within the scope of the Technology Acceptance Model [27] More online sessions of SLTs, who reported that they had been satisfied with using their clinical skills in telepractice, emphasized how important perceived usefulness and utility were on attitudes. This finding was consistent with the findings of some telepractice (telepractice, telerehabilitation) studies [4, 38-41]. It became prominent once again that the more clinicians take a technology useful, the easier it is to adapt to these technologies. This finding provided clinical implications for what kind of incentive studies could be done for SLTs to easily switch to telepractice services. It can provide evidence, in-service trainings, models and supervision for the effectiveness of the method in developing the first attitudes of SLTs towards telepractice.

Considering the platforms preferred by the participants to use during telepractice applications, it was seen that they mostly conducted telepractice sessions via the Zoom application. Then, the two most frequently used softwares were Whatsapp (video call) and Skype. FaceTime, Adobe Connect and other software were found to be the last and equally preferred in terms of usage frequency. In spite of this situation, in a qualitative study in the literature, thoughts about the usage and accessibility of Adobe Connect software were reported [42]. The fact that the standard version of Zoom is free to use in one-to-one calls and is easy to use compared to software such as Adobe Connect and Webex may have led the participants to this pref-

erence. The issue that needs to be emphasized here is the importance of the "perceived convenience" factor within the scope of the Technology Acceptance Model [27]. The easier the usage of these systems is perceived in the beginning, the more positive user attitudes are [38] In their study, Bradford *et al*. [14] stated that most of the practitioners whose opinions they received initially doubted that telepractice would be effective and thought that the therapeutic relationship could not be established, but they concluded that their negative opinions on this issue changed in the opposite direction as the telepractice sessions progressed. Similarly, in our study, SLTs who performed telepractice sessions before the pandemic did not have any difficulty in providing telepractice services during the pandemic process.

SLTs reported that they most frequently used the standard version of Zoom, WhatsApp and Skype in telepractice. However, all these platforms do not have HIPAA (Health Insurance Portability and Accountability Act) certification. According to ASHA [5], the first issue that SLTs should look into when choosing these platforms is whether the systems have this security certificate. In this way, the security of the data regarding the client, the therapist or the service used will be ensured. Another issue considered secondary is that WhatsApp and Skype do not have file sharing and whiteboard features. This situation makes the applied telepractice more limited. Apart from the software used in providing telepractice service, technical issues are also important.

In this study, the most common technological problems that SLTs experienced during service delivery were internet disconnections, sound problems and video problems. These problems are highly anticipated problems in online usage in line with the literature [4, 43, 24]. Thus, the necessity of in-service training and how important it is to provide guidance and guides to SLTs revealed once again.

In this study, no relationship was found between the ages of SLTs and the frequency of telepractice sessions during the pandemic period. However, there are opinions that there is a relationship between these variables [18]. In Turkey, the SLT area is a developing area and an important part of personnel serving in this field is under 30 years of age. Thus, it was not possible to examine all participants by dividing them into certain age groups (eg, 20-40 and 40-60). It may be suggested future studies to examine the subject by considering different age groups.

SLTs reported the disorders in which telepractice can be used most effectively as speech voice disorders, fluency disorders and voice disorders, respectively. The least appropriate disorder was swallowing disorders. This situation is mostly compatible with the literature. In the field of research, it is seen that the disorders in which telepractice is effective are SSD [44, 45], fluency disorders [4, 15, 46, 47] and vocal disorders [13, 48-51] similar to our study. However, it is seen that there are many effectiveness studies in the literature, from autism [52-54] to swallowing disorder [55-57]. However, at this point, findings regarding user perspectives in terms of clients and clinicians in qualitative research are also extremely important. In this context, qualitative studies are also needed to determine the disorders for which telepractice is appropriate.

It was observed that the satisfaction levels of SLTs regarding the therapeutic relationship in telepractice were answered almost equally as "almost not satisfied", "partially satisfied" and "satisfied". This situation showed that the level of satisfaction of SLTs with the therapeutic relationship with the clients was not very high. In some studies in the literature, it was stated that the therapeutic relationship between the therapist and the client could be negatively affected in telepractice [28, 42, 58]. However, in telepractice, the therapeutic relationship between the client and the therapist needs to be studied in more detail. For example, although it was reported that telepractice might have some disadvantages in terms of therapeutic relevance [4], it is also important to examine which factors (e.g., clinician skills, natural approaches) minimize this disadvantage.

There was a significant relationship between the number of sessions that SLTs did in the last month and their level of using the skills of the clinician. With this finding, it was seen that the thoughts of SLTs on their level of using clinician skills were related to the number of sessions they had done. In this context, the increase in the telepractice experience of the therapist may lead to an increase in positive thoughts about the better use of the clinician's skills. In other words, it can be said that as the therapist's familiarity with the

new service increases, he/she can use his/her skills regarding that service better over time.

With the increase in the number of sessions done by SLTs during the pandemic, their satisfaction level with the telepractice service they offer also increased. Especially in the high satisfaction level of the telepractice service they provide, e-helpers were of great importance. In this study, the most frequently needed disorder groups were SSD, DSL and autism etc. The younger age of the individuals in the relevant disorder groups may create a disadvantage in the processes of adapting and maintaining their cognitive or physical abilities to the service offered in front of the telepractice screen. This finding may be based on the assumption that the auxiliary support of SLTs in telepractice can facilitate efficient gain in the client. Moreover, it was found that SLTs had the most telepractice sessions with children aged 7-11 and 4-6, respectively. Considering that the disorder groups presenting in these age groups were disorders such as SSD, DSL and autism, it was seen that SLTs performed telepractice in the group where auxiliary support was most needed. However, the age groups that SLTs found most suitable for telepractice were 12-21, 22-64 and 7-11 years. An important reason why SLTs found these age groups suitable for telepractice may be that they do not need adult support in telepractice sessions applied for these age groups.

Finally, most of the participants stated that they did not do group therapy in telepractice applications before. Furthermore, half of the participants thought that telepractice was suitable for group therapy, while the other half stated that it was not. Group therapies differ in terms of therapy dynamics compared to individual therapies and contain different interaction elements. While individual therapies are based solely on client-therapist interaction, group therapies are based on the interaction of clients with one another and with the therapist. Since achieving these dynamics may require experience and competence for the therapist in telepractice processes compared to in-person therapy, SLTs may exhibit a timid attitude regarding the application of group therapy in telepractice.

## CONCLUSION AND RECOMMENDATIONS

It was revealed that for SLTs, first trials on teleconferencing platforms and familiarity with the method were decisive in future preferences for using telepractice. Using these systems for social purposes or to provide therapy services, SLTs were able to adapt to provide these services at an early stage even in a difficult period such as the COVID-19 pandemic. This finding supports the model [27] that TAM's "perceived easiness" will positively affect future attitudes. At this point, it may be persuasive that professional organizations such as DKTD (ASLT) [3] provide guidelines for clinicians, model demonstrations of practices and evidence of effectiveness. Implementation protocols, practical trainings and guidelines for dealing with potential problems can accelerate this adaptation process, taking into account factors such as the current conditions of the country's legal, cultural or SLT field.

According to the SLTs, telepractice is not suitable for many client groups. As research evidence showed, telepractice can be used as an effective means of serving a variety of client groups, from autism to swallowing disorders, when properly prepared [22, 59, 60]. At this point, factors such as multiple disabilities, mobility, cooperation, and the importance of e-helpers came to light in candidate clients for telepractice.

It was also observed that the teleconferencing platforms used by SLTs were not compatible with ASHA [6] guidelines. SLTs probably preferred the software they were most familiar with and the easiest to use. However, according to ASHA [6], the most critical issue in software selection is the use of HIPAA compliant softwares that ensures the security of health-related data. Beyond that, the lack of features such as screen sharing and whiteboards in these softwares used will reduce the quality of the service provided.

The finding related to using clinician skills in telepractice can be evaluated in the context of TAM's perceived usefulness [27]. As SLTs believe that they use their skills effectively in telepractice, their attitudes towards the method will become more positive. Here again, clinicians should be provided with guidance and supervision on how to use the skills they use in the online environment as well, just like in in-person therapy.

*Authors' Contribution*

Study Conception: MEC; Study Design: MEC, İCY, AI; Supervision: MEC; Funding: MEC, İCY, AI; Materials: MEC, İCY; Data Collection and/or Processing: MEC, İCY; Statistical Analysis and/or Data Inter-

pretation: MEC, İCY, AI; Literature Review: MEC, İCY, AI; Manuscript Preparation: MEC, İCY, AI and Critical Review: MEC, İCY, AI.

*Conflict of interest*

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# Type, source, adequacy and outcome of consultations requested from the department of general surgery: a retrospective cohort study

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## ABSTRACT

**Objectives:** To evaluate consultations requested from the department of general surgery in terms of type, source and adequacy and outcome regarding general surgery practice.

**Methods:** A total of 4706 consultations requested from the department of general surgery during the 2019 calendar year were included in this retrospective study. Data on patient demographics, type of consultation (urgent, routine), the requesting clinic, time of request, response time to consultation request (min), diagnosis and management of consulted patients by general surgery clinic and survivorship status were recorded.

**Results:** Consultations were urgent (69.0%) and made outside office hours (66.0%) in most of cases and more commonly requested by the emergency department (67.5%). The surgical pathology was confirmed only in 1338 (28.4%) consultations, while more commonly for urgent vs. routine requests (37.4 vs. 8.5%, $p = 0.001$), for consultations requested by emergency department (ranged 30.9 to 40.0%) vs. other clinics (ranged 0.0% to 19.1%, $p = 0.001$) and for diseases of colon-rectum-anus (100.0%, $p = 0.001$) than other disorders. The likelihood of urgent consultations (72.0% vs. 37.3%, $p = 0.001$) and post-consultation inpatient management (90.5% vs. 24.7%, $p = 0.001$) and were more likely among survivors vs. non-survivors.

**Conclusions:** In conclusion, our findings revealed that most of the consultations were urgent, outside the office hours and outpatient consultations requested by the emergency department, while surgical pathology was confirmed only in one third of consultations. Our findings indicate improved consultation practice particularly for routine requests by non-emergency clinics to prevent the incompatible or unnecessary consultation requests and related healthcare resource utilization.

**Keywords:** Consultation request, general surgery, urgent, routine, adequacy of request

Specialty consultation is a critical aspect of healthcare practice in terms of provision of the high-quality medical and surgical services via follow-up and treatment of a patient in accordance with clinical knowledge, experience and recommendations of consultant doctor related to the specific condition that requires care beyond the scope of the clinic in charge of the patient [1-4].

Specialty consultation also considered a laborious task necessitating appropriate specialist triage to ensure timely evaluation of consulted patients as well as appropriate co-management between primary care and specialty care, given the likelihood of potential hazards (i.e. life-threatening outcomes, legal issues) in case of consultation delays 1, 4-6].

General surgery is the most comprehensive surgi-

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cal discipline that deals a wide range of diseases [3], while surgical yield is considered a unique measure of efficiency among surgical services that shows the percentage of ambulatory surgical consultations resulting in a scheduling of an operative intervention [6, 7].

This single center retrospective study was therefore designed to evaluate consultations requested from the department of general surgery during the 2019 calendar year at a tertiary care hospital in terms of type and source of consultations as well as their adequacy and outcome regarding general surgery practice.

## METHODS

### Study Population

In this retrospective study, a total of 4706 electronic consultations (mean age: 53.7 ± 21.3) years, 54% were females) requested from the department of general surgery at hospital between January 1st 2019 and December 31st 2019 were included.

The study was conducted in full accordance with local Good Clinical Practice (GCP) guideline and current legislations, while the permission was obtained from the institutional ethics committee for the use of patient data for publication purposes (Date of Approval: 5/02/2020; Reference number/Protocol No:2020/0088). The work has been reported in line with the STROCSS criteria [8] and was registered by Research Registry with the Unique Identifying Number 5998.

### Hospital Characteristics

The study hospital is a 660-bed tertiary university hospital located in a city within the metropolitan area and serving for all medical specialties including a single general surgery clinic for entire surgery sub-specialties as well as anesthesia and internal medicine intensive care units.

### Assessments

Data on patient demographics (age, gender), type of consultation (urgent, routine), the requesting clinic, time of request, response time to consultation request (min), type of admission, diagnosis and management of consulted patients by general surgery clinic and survivorship status were retrieved from hospital records. Patient demographics and consultation parameters were evaluated with respect to confirmation of operative or non-operative surgical pathology (yes vs. no) after consultation, general surgery ward hospitalization (yes vs. no) and type of consultation made by the consulting service based on indication (urgent vs. routine).

### Statistical Analysis

Statistical analysis was made using NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA). Pearson Chi-square test, Fisher's exact test and Fisher-Freeman-Halton tests were used for the comparison of categorical data, while numeric data were analyzed using Student-t test and Mann-Whitney U test depending on the normality findings. Data were expressed as mean± standard deviation (SD), median (minimum-maximum) and percent (%) where appropriate. $P < 0.05$ was considered statistically significant.

## RESULTS

### *Overall Characteristics*

Overall, mean patient age was 53.7 (range, 17 to 102) years, and 2541 (54.0%) of 4706 consultations were requested for female patients. The median response time to the consultation was 89 (range, 20 to 1440) min. Consultations were urgent (69.0%) and made outside office hours (66.0%) in most cases and more commonly requested by the emergency department (67.5%, 45.9% from green zone) and mostly for outpatients (68.5%) and upper GI disorders (58.7%) (Table 1). The surgical pathology was confirmed only in 1338 (28.4%) consultations, while for 3368 (71.6%) consultations there was no surgical pathology or need for treatment by general surgery physicians. Of 1338 consultations with confirmed surgical pathology, 1086 (81.2%) were managed on an inpatient basis in the general surgery ward, while the treatment decisions involved medical treatment in 49.2% of cases, surgical treatment in 36.8% of cases, and transfer to another clinic in 14% of patients. Overall, mortality occurred in 394 (8.4%) of 4706 consultations patients and 190 (48.2%, 14.2% of those with surgical pathology) were patients with confirmed surgical pathology (Table 1).

### *Study Variables According to Confirmation of Surgical*

**Table 1. Study variables according to confirmation of surgical pathology after consultation**

| | | Total | Confirmation of a surgical pathology | | |
|---|---|---|---|---|---|
| | | | No | Yes | *p* value |
| **Age (year)** | Mean ± SD | 53.7 ± 21.3 | 54.0 ± 21.3 | 53.1 ± 21.3 | 0.197[a] |
| | Median (min-max) | 54 (17-102) | 54 (17-102) | 53.5 (18-96) | |
| **Gender, n (%)** | Female | 2541 (54.0) | 1942 (76.4) | 599 (23.6) | **0.001**[b] |
| | Male | 2165 (46.0) | 1426 (65.9) | 739 (34.1) | |
| **Type of consultation, n (%)** | Urgent | 3250 (69.0) | 2036 (62.6) | 1214 (37.4) | **0.001**[b] |
| | Routine | 1456 (30.9) | 1332 (91.5) | 124 (8.5) | |
| **Requested by, n (%)** | Emergency department (green zone) | 2158 (45.9) | 1294 (60.0) | 864 (40.0) | **0.001**[b] |
| | Emergency department (yellow zone) | 962 (20.4) | 637 (66.2) | 325 (33.8) | |
| | Emergency department (red zone) | 55 (1.2) | 38 (69.1) | 17 (30.9) | |
| | Internal medicine | 737 (15.7) | 642 (87.1) | 95 (12.9) | |
| | Anesthesia | 94 (2.0) | 76 (80.9) | 18 (19.1) | |
| | Obstetrics and Gynecology | 319 (6.8) | 310 (97.2) | 9 (2.8) | |
| | Infectious diseases | 68 (1.4) | 65 (95.6) | 3 (4.4) | |
| | Neurosurgery | 38 (0.8) | 38 (100.0) | 0 (0.0) | |
| | Neurology | 41 (0.9) | 41 (100.0) | 0 (0.0) | |
| | Orthopedics | 70 (1.5) | 65 (92.9) | 5 (7.1) | |
| | Urology | 85 (1.8) | 84 (98.8) | 1 (1.2) | |
| | Other | 79 (1.7) | 78 (98.7) | 1 (1.3) | |
| **Time of request, n (%)** | Within office hours | 1600 (34.0) | 1233 (77.1) | 367 (22.9) | **0.001**[b] |
| | Outside office hours | 3106 (66.0) | 2135 (68.7) | 971 (31.3) | |
| **Type of admission, n (%)** | Outpatient | 3223 (68.5) | 2017 (62.6) | 1206 (37.4) | **0.001**[b] |
| | Inpatient | 1483 (31.5) | 1351 (991.1) | 132 (8.9) | |
| **Diagnosis, n (%)** | Upper GI disorder | 2761 (58.7) | 1810 (65.6) | 951 (34.4) | **0.001**[b] |
| | Hepatobiliary disorder | 281 (6.0) | 151 (53.7) | 130 (46.3) | |
| | Colon, rectum, anus disorder | 107 (2.3) | 0 (0.0) | 107 (100.0) | |
| | Trauma | 210 (4.5) | 160 (76.2) | 50 (23.8) | |
| | Skin-soft tissue disorder | 131 (2.8) | 121 (92.4) | 10 (7.6) | |
| | Other | 1216 (25.8) | 1126 (92.6) | 90 (7.4) | |
| **Hospitalization after consultation, n (%)** | No | 3620 (76.9) | 3368 (93.0) | 252 (7.0) | **0.001**[b] |
| | Yes | 1086 (23.1) | 0 (0.0) | 1086 (100.0) | |
| **Treatment plan, n (%)** | Medical treatment | 658 (14.0) | 0 (0.0) | 658 (100.0) | **0.001**[b] |
| | Surgery | 492 (10.5) | 0 (0.0) | 492 (100.0) | |
| | Transfer to another ward | 392 (8.3) | 204 (52.0) | 188 (48.0) | |
| | No need for treatment by GS | 3164 (67.2) | 3164 (100.0) | 0 (0.0) | |
| **Mortality, n (%)** | No | 4312 (91.6) | 3164 (73.4) | 1148 (26.6) | **0.001**[b] |
| | Yes | 394 (8.4) | 204 (51.8) | 190 (48.2) | |
| **Response time to consultation (min)** | Mean ± SD | 116.7 ± 103.2 | 117.7 ± 102.2 | 114.2(105.7) | 0.115[c] |
| | Median (min-max) | 89 (20-1440) | 89 (20-1440) | 88 (20-1440) | |

[a]Student-t test; [b]Pearson Chi-Square test; [c]Mann Whitney U test

### *Pathology*

Amongst the consultations requested from the department of general surgery, confirmation of a surgical pathology was significantly more likely for male vs. female patients (34.1 vs. 23.6%, $p = 0.001$), for urgent vs. routine requests (37.4 vs. 8.5%, $p = 0.001$), for consultations requested by emergency department (ranged from 30.9 % in red zone to 40.0% in green zone) vs. other clinics (ranged 0.0% to 19.1%, $p = 0.001$) as well as those requested by internal medicine (12.9%) and anesthesia (19.1%) vs. clinics other than emergency department (ranged 0.0% to 7.1%, $p = 0.001$) (see Table 1). Confirmation of surgical pathology was also more likely for consultation requests made outside vs. within office hours (31.3 vs. 22.9%, $p = 0.001$) and for consultations requested for outpatients vs. inpatients (37.4 vs. 8.9%, $p = 0.001$) (Table 1). The likelihood of confirmed surgical pathology was higher for gastrointestinal disorders (ranged 34.4% to 100.0) vs. trauma (23.9%), soft tissue (7.6%) and other (7.4%) disorders, and for trauma vs. soft tissue and other disorders ($p = 0.001$). Specifically, diseases of colon-rectum-anus (100.0%) were associated with the highest likelihood of confirmed surgical pathology, as followed by hepatobiliary disorder (46.3%), upper GI disorder (34.4%) and trauma (23.8%) ($p = 0.001$) (see Table 1). Consultations resulted in confirmed surgical pathology were more likely to managed on an inpatient basis than on an outpatient basis (100 vs. 7.0%, $p = 0.001$) and also with medical or surgical treatment (100.0% for each) rather than transfer to another ward (48.0%) ($p = 0.001$) (see Table 1). The likelihood of a confirmed surgical pathology was higher among non-survivors vs. survivors (48.2 vs. 26.6%, $p = 0.001$), while no significant difference was noted in the likelihood of confirmed surgical pathology after consultations in terms of patient age and response time to consultation (see Table 1).

### *Study Variables According to General Surgery Ward Hospitalization*

Inpatient management via hospitalization at general surgery ward was more likely for consultations requested for younger vs. older patients (mean age: 51.7 ± 20.8) vs. 58.9 ± 22.6 years, $p = 0.001$), for outpatients vs. inpatients (85.1 vs. 45.5%, $p = 0.001$) and for urgent vs. routine requests (84.6 vs. 47.6%, $p = 0.001$). Consultations requested by emergency (green zone, 99.4%) and obstetrics-gynecology (88.9%) departments were associated with highest rate of hospitalization at a general surgery ward, as followed by those requested by yellow zone (76.6%) and red zone (76.5%) emergency, internal medicine (46.3%) and anesthesia (22.2%) departments ($p = 0.001$) (Table 2). The skin-soft tissue disorders (100.0%) were associated with the highest (100.0%) likelihood of hospitalization, as followed by upper GI disorder (87.2%), hepatobiliary disorder (86.2%) and trauma (84.0%), while likelihood of hospitalization was lowest for diseases of colon-rectum-anus (6.5%) ($p = 0.001$). Hospitalization was required for all of upper GI, hepatobiliary and hernia surgeries, whereas only for 40.0% of proctology surgeries ($p = 0.001$) (see Table 2). General surgery ward hospitalization was also more likely in survivors vs. non-survivors vs (90.5% vs. 24.7%, $p = 0.001$), while no significant difference was noted in the likelihood of hospitalization in terms of patient gender, time of request and response time to consultation (see Table 2).

### *Study Variables According to Type of Consultation*

Urgent vs. routine general surgery consultations were associated with younger patient age (51.6 ± 21.5 vs. 58.4 ± 20.3 years, $p = 0.001$), predominance of requests by emergency department (ranged 99.8 to 100.0%) than by other clinics (ranged 0.0 t 16.3%, $p = 0.001$), higher rates of outside than within office hours requests (79.8 vs. 48.1%, $p = 0.001$), outpatient than in-patient admissions (99.7 vs. 2.5%, $p = 0.001$) and presence than absence of inpatient management by general surgery clinic (94.6 vs. 61.4%, $p = 0.001$) (Table 3). The likelihood of urgent consultations was significantly higher for colon, rectum, anus disorders (98.1%) and upper GI disorder (87.3%) than for hepatobiliary disorder (60.9%), skin-soft tissue disorder (65.6%) and trauma (69.0%) ($p = 0.001$). Urgent vs. routine general surgery consultations were associated with higher rate of medical (95.9%) or surgical treatment (93.5%) than transfer to another ward (37.8%) (see Table 3). Urgent vs. routine consultations (72.0% vs. 37.3%, $p = 0.001$) were more likely among survivors vs. non-survivors, and associated with lower response time to consultation request (median 77 vs. 122 min, $p = 0.001$), while no significant difference was noted in the likelihood of hospitalization in terms of

**Table 2. Study variables according to hospitalization after consultation**

| | | Hospitalization at general surgery ward | | |
|---|---|---|---|---|
| | | **No (n = 252)** | **Yes (n = 1086)** | ***p* value** |
| **Age (year)** | Mean ± SD | 58.9 ± 22.6 | 51.7 ± 20.8 | **0.001**[a] |
| | Median (min-max) | 63.5 (18-92) | 52 (18-96) | |
| **Gender, n (%)** | Female | 116 (19.4) | 483 (80.6) | 0.654[b] |
| | Male | 136 (18.4) | 603 (81.6) | |
| **Type of consultation, n (%)** | Urgent | 187 (15.4) | 1027 (84.6) | **0.001**[b] |
| | Routine | 65 (52.4) | 59 (47.6) | |
| **Requested by, n (%)** | Emergency department (green zone) | 100 (11.6) | 764 (88.4) | **0.001**[c] |
| | Emergency department (yellow zone) | 76 (23.4) | 249 (76.6) | |
| | Emergency department (red zone) | 4 (23.5) | 13 (76.5) | |
| | Internal medicine | 51 (53.7) | 44 (46.3) | |
| | Anesthesia | 14 (77.8) | 4 (22.2) | |
| | Obstetrics and Gynecology | 1 (11.1) | 8 (88.9) | |
| | Infectious diseases | 3 (100.0) | 0 (0.0) | |
| | Orthopedics | 3 (60.0) | 2 (40.0) | |
| | Urology | 0 (0.0) | 1 (100.0) | |
| | Other | 0 (0.0) | 1 (100.0) | |
| **Time of request, n (%)** | Within office hours | 78 (21.3) | 289 (78.7) | 0.164[b] |
| | Outside office hours | 174 (17.9) | 797 (82.1) | |
| **Type of admission, n (%)** | Outpatient | 180 (14.9) | 1026 (85.1) | **0.001**[b] |
| | Inpatient | 72 (54.5) | 60 (45.5) | |
| **Diagnosis, n (%)** | Upper GI disorder | 122 (12.8) | 829 (87.2) | **0.001**[b] |
| | Hepatobiliary disorder | 18 (13.8) | 112 (86.2) | |
| | Colon, rectum, anus (proctology) | 100 (93.5) | 7 (6.5) | |
| | Trauma | 8 (16.0) | 42 (84.0) | |
| | Skin-soft tissue disorder | 0 (0.0) | 10 (100.0) | |
| | Other | 4 (4.4) | 86 (95.6) | |
| **Type of surgery, n (%)** | Upper GI | 0 (0.0) | 343 (100.0) | **0.001**[c] |
| | Hepatobiliary | 0 (0.0) | 87 (100.0) | |
| | Hernia surgery | 0 (0.0) | 42 (100.0) | |
| | Proctology | 9 (60.0) | 6 (40.0) | |
| | Other | 2 (13.3) | 13 (86.7) | |
| **Mortality, n (%)** | No | 109 (9.5) | 1039 (90.5) | **0.001**[b] |
| | Yes | 143 (75.3) | 47 (24.7) | |
| **Response time (min)** | Mean ± SD | 116.4 ± 123.9 | 113.6 ± 101.0 | 0. 892[d] |
| | Median (min-max) | 85.5 (20-1440)) | 89 (20-1440) | |

[a]Student-t test; [b]Pearson Chi-Square test; [c]Fisher Freeman Halton test; [d]Mann Whitney U test

**Table 3. Study variables according to type of consultation**

| | | Type of consultation | | |
|---|---|---|---|---|
| | | **Urgent (n = 3250)** | **Routine (n = 1456)** | ***p* value** |
| **Age (year)** | Mean ± SD | 51.6 ± 21.5 | 58.4 ± 20.3 | **0.001**[a] |
| | Median(min-max) | 51 (18-102) | 60 (17-96) | |
| **Gender, n (%)** | Female | 1726 (67.9) | 815 (32.1) | 0.068[b] |
| | Male | 1524 (70.4) | 641 (29.6) | |
| **Requested by, n (%)** | Emergency department (green zone) | 2157 (100) | 1 (0) | **0.001**[b] |
| | Emergency department (yellow zone) | 960 (99.8) | 2 (0.2) | |
| | Emergency department (red zone) | 55 (100) | 0 (0) | |
| | Internal medicine | 18 (2.4) | 719 (97.6) | |
| | Anesthesia | 2 (2.1) | 92 (97.9) | |
| | Obstetrics and Gynecology | 52 (16.3) | 267 (83.7) | |
| | Infectious diseases | 0 (0) | 68 (100) | |
| | Neurosurgery | 1 (2.6) | 37 (97.4) | |
| | Neurology | 2 (4.9) | 39 (95.1) | |
| | Orthopedics | 0 (0) | 70 (100) | |
| | Urology | 0 (0) | 85 (100) | |
| | Other | 3 (3.8) | 76 (96.2) | |
| **Time of request, n (%)** | Within office hours | 770 (48.1) | 830 (51.9) | **0.001**[b] |
| | Outside office hours | 2480 (79.8) | 626 (20.2) | |
| **Type of admission, n (%)** | Outpatient | 3213 (99.7) | 10 (0.3) | **0.001**[b] |
| | Inpatient | 37 (2.5) | 1446 (97.5) | |
| **Diagnosis, n (%)** | Upper GI disorder | 2409 (87.3) | 352 (12.7) | **0.001**[b] |
| | Hepatobiliary disorder | 171 (60.9) | 110 (39.1) | |
| | Colon, rectum, anus (proctology) | 105 (98.1) | 2 (1.9) | |
| | Trauma | 145 (69.0) | 65 (31) | |
| | Skin-soft tissue disorder | 86 (65.6) | 45 (34.4) | |
| | Other | 334 (27.5) | 882 (72.5) | |
| **Hospitalization after consultation, n (%)** | No | 2223 (61.4) | 1397 (38.6) | **0.001**[b] |
| | Yes | 1027 (94.6) | 59 (5.4) | |
| **Treatment plan, n (%)** | Medical treatment | 631 (95.9) | 27 (4.1) | **0.001**[b] |
| | Surgery | 460 (93.5) | 32 (6.5) | |
| | Transfer to another ward | 148 (37.8) | 244 (62.2) | |
| | No need for treatment by GS | 2011 (63.6) | 1153 (36.4) | |
| **Type of surgery, n(%)** | Upper GI | 318 (92.7) | 25 (7.3) | 0.800[c] |
| | Hepatobiliary | 82 (94.3) | 5 (5.7) | |
| | Hernia surgery | 41 (97.6) | 1 (2.4) | |
| | Proctology | 14 (93.3) | 1 (6.7) | |
| | Other | 14 (93.3) | 1 (6.7) | |
| **Mortality, n (%)** | No | 3103 (72.0) | 1209 (28) | **0.001**[b] |
| | Yes | 147 (37.3) | 247 (62.7) | |
| **Response time (min)** | Mean ± SD | 101.8 ± 84.0 | 149.9 ± 130.7 | **0.001**[d] |
| | Median (min-max) | 77 (20-704) | 122 (20-1440) | |

[a]Student-t test; [b]Pearson Chi-Square test; [c]Fisher Freeman Halton test; [d]Mann Whitney U test

patient gender and type of surgery (see Table 3).

## DISCUSSION

The current analysis of overall consultations requested from the department of general surgery during the 2019 calendar year at a tertiary care hospital revealed that most of consultations to be urgent outpatient consultations related to upper GI disorders and to be requested outside the office hours and by emergency department in most of cases. Notably, the surgical pathology was confirmed only in one third of consultations, while two third of consultations requested from the department of general surgery were not associated with a surgical pathology or a need for treatment by general surgeons. Majority of consultations with confirmed surgical pathology were managed on an inpatient basis in the general surgery ward either with medical or surgical treatment.

Our findings seem in accordance with data from a recent study in Turkey regarding the analysis of 221 consultations requested from the department of general surgery over 6-month, which indicated that majority (91.9%) of consultations were requested by the emergency services and the rate of patients who were found to have surgical disease was 33% [3]. This emphasizes the considerably high possibility of a consultation requested from the department of general surgery not to be associated with a confirmed surgical pathology. Nonetheless, while high rates of inappropriate consultations which resulted in no need for management by general surgeon in our cohort seems notable, it should be noted that urgent outside-office-hours consultations and consultations requested by emergency department were more likely to be confirmed with surgical pathology after reviewed by general surgeons. Hence, the consultation practice should be improved particularly for the routine within-office-hours consultations as requested by clinics other than emergency service.

Accordingly, in the current study, urgent consultations and those related to proctology were both more likely to have a surgical diagnosis after general surgery assessment, while basically treated on an inpatient and an outpatient basis, respectively. This seems in line with well-established efficacy, safety and tolerability of day care proctological procedures a strategy that reduces costs and release beds for major surgeries without increasing morbidity or mortality [9, 10].

Notably, general surgery consultations for lower GI disorders were more likely to be associated with confirmed surgical pathology than those for upper GI and hepatobiliary disorders as well as those for trauma, while the lowest rate of confirmation was evident for consultation related to skin-soft tissue disorders. This seems also notable given that when confirmed to be associated with a surgical pathology after consulted by general surgeon, the main treatment strategy seems to be an outpatient management in case of lower GI disorders, whereas an inpatient management for all other disorders. Moreover, urgent consultations and inpatient management of confirmed surgical pathologies were more common among survivors.

Indeed, upper gastrointestinal bleeding per se comprised nearly two thirds of consultations requested from the department of general surgery in our study. Although this seems in accordance with consideration of acute upper gastrointestinal bleeding is very a common medical emergency [11], surgical pathology was confirmed only in one third of these cases when consulted by a general surgeon. Thus, our findings emphasize likelihood of incompatible or unnecessary consultations to be requested from the department of general surgery particularly in case of suspected upper gastrointestinal bleeding, possibly in relation to avoid a delayed endoscopy referral as early endoscopy within 24 h of admission has strongly been recommended by the international guidelines [12, 13].

In the current study, trauma comprised less than 5% of consultations requested from the department of general surgery, which seems to be related to location of the study hospital in an exurban area outside major metropolitan with relatively low traffic accident or crime rates.

The higher rate of mortality among consulted patients who subsequently managed via medical treatment rather than surgery seems to be in accordance with higher mortality, re-admission and consultation/referral rates reported in patients admitted to surgical departments who are not operated than those operated, as associated with greater medical complexity and urgency of admission in these patients [14]. Hence the association of urgent consultations with lesser likelihood of mortality seems also consis-

tent with the fact that they were managed by hospitalization to general surgery ward in most of cases.

Although the lower response time to urgent vs. routine consultations in our study support that the urgency of the patient is the most important factor affecting the duration of consultation [15], median response time of 77 min seems longer than the recommended 30-minute response period for urgent consultations [16]. Similarly, in a past study on consultations requested by emergency department in Turkey, authors also noted a longer than expected response time (median: 96 min) for urgent consultations [16]. Although prolonged response time to urgent consultations requested by an emergency department has been considered to adversely affect the operation of the emergency service [16], response time to consultation from general surgery was not associated with likelihood of consultation to result in confirmed surgical pathology or inpatient management by general surgery in our study.

Possibility of inappropriateness of required consultation was also reported in other departments; for example, in a 2-year retrospective study regarding 338 consultations requested from pulmonary diseases department authors reported that majority of the consultations were from the emergency department, while confirmation of pathology regarding pulmonary diseases was evident only in 42% of consultations [17].

High-functioning healthcare systems aim to safely optimize surgical yield, with the highest percentage of ambulatory general surgery patients receiving indicated elective surgery without any need for unanticipated emergent or urgent interventions [6]. Thus, consultations requested from the department of general surgery should also comply with the best practice in surgical care delivery in terms of enabling the patients who would most benefit from a surgical intervention to be evaluated by surgical clinicians during limited ambulatory clinic visit times and scheduled for surgery and those who would not benefit from a surgical intervention to remain in primary care [6].

Indeed, in past study of 1743 electronic consultations submitted to general surgery, authors reported the association of using an integrated electronic consultation and referral system (in which all referrals are submitted electronically and reviewed by a general surgery clinician) with a significant increase in the rate of patients scheduled for a subsequent surgical intervention and thus surgical yield of an ambulatory general surgery service (from 35% to 46%) [6].

Notably, the request of consultation after proper triage and evaluation by the responsible physician based on predefined written algorithms, as well as continuous evaluation and follow-up of the quality of consultation service by each clinic are considered important steps to prevent the incompatible or unnecessary consultation requests [6, 16].

It should also be emphasized that on the basis of knowledge and practice on general surgery gained during medical education, emergency department or outpatient physicians are in fact capable of discriminating non-urgent general surgery issues that could be referred directly to outpatient clinic instead of requiring a formal consult by the inpatient service. Hence, unnecessary consultations seem to be prevalent due to malpractice concern or low self-confidence, and improved consultation practice in terms of these concerns seems important given its potential impact on efficiency and patient care.

### Limitations

Certain limitations to this study should be considered. First, due to the retrospective design it is impossible to establish any cause-and-effect relationships. Second, potential lack of generalizability seems another important limitation due to single-center design.

## CONCLUSION

In conclusion, this retrospective analysis of consultations requested from the department of general surgery during the 2019 calendar year at a tertiary care hospital revealed that most of the consultations were urgent, outside the office hours and outpatient consultations requested by the emergency department. The surgical pathology was confirmed only in one third of consultations, while urgent consultations and those related to proctology were both more likely to have a surgical diagnosis after general surgery assessment and basically treated on an inpatient and an outpatient basis, respectively. Moreover, urgent consultations and inpatient management of confirmed surgical pathologies were more common among survivors. Our findings indicate improved consultation practice and in-clinic feedback assessment of quality of requested consultations, particularly for routine requests and re-

quest by clinics other than emergency service to enable surgical evaluation for the patients who would most benefit from a surgical intervention and thereby to increase the efficiency of consultation practice by preventing the incompatible or unnecessary consultation requests and related healthcare resource utilization.

*Authors' Contribution*

Study Conception: ML, OA; Study Design: ML, OA; Supervision: ML, OA; Funding: ML, OA; Materials: ML, OA; Data Collection and/or Processing: ML, OA; Statistical Analysis and/or Data Interpretation: ML, OA; Literature Review: ML, OA; Manuscript Preparation: ML, OA and Critical Review: ML, OA.

*Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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# Hypofibrinogenemia caused by tigecycline use in a patient with acute cholecystitis: a case report and review of the literature

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## ABSTRACT

**Objectives:** Tigecycline is the first member of glicylcycline class of antibiotics, which has a broad spectrum of action. In previous reports, coagulopathy and hypofibrinogenemia caused by tigecycline use was described. We aimed to present a case of hypofibrinogenemia in association with tigecycline use. A 79-years-old male was admitted to medical intensive care unit for acute cholecystitis and acute renal failure. He had no history of coagulation disorder. He was receiving meropenem for septic shock on the admission. On the 7th day of meropenem, his infection didn't improve and fever continued. Because of that tigecycline was added to treatment. Patient's infection parameters improved, his fever dropped under treatment, but his prothrombin time, international normalized ratio and activated partial thromboplastin time levels increased and fibrinogen level decreased (0.96 g/L). Tigecycline was discontinued that day. On the fifth day after cessation of tigecycline, his fibrinogen levels and other coagulation parameters returned to normal ranges. The mechanisms of coagulopathy and hypofibrinogenemia should be elucidated in futher studies. We strictly suggest, regular monitoring of coagulation parameters in patients receiving tigecycline treatment.

**Keywords:** Tigecycline, hypofibrinogenemia, adverse effect, coagulopathy, antibiotics

Tigecycline is the first member of glicylcycline class of antibiotics, which is structurally similar to tetracyclines. It has broad spectrum activity, particularly against multi-drug resistant bacteria (e.g Methicillin resistant *Staphylococcus aureus*, vancomycin resistant enterococcus, *Acinetobacter baumannii*) [1, 2]. It is indicated in patients who are 18 years or older for complicated intraabdominal infections, complicated skin and skin structure infections and community acquired pneumonia [3]. Tigecycline was well tolerated in registry trials, with the exception of increased rates of nausea and vomiting. But after post-marketing data signaling increased mortality rates in tigecycline treated patients have brought its use in patients with complicated infections into question, prompting other clinicians to consider other potential adverse effects which was not found in initial studies [4]. Some previous case reports showed that tigecycline seems to cause coagulation disorders, which manifested with bleeding or abnormalities in coagulation paremeters [1-5]. In this report we presented a case of hipofibrinogenemia in a patient treated with tigecycline.

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## CASE PRESENTATION

A 79-year-old male who had a history of diabetes, hypertension, congestive heart failure and chronic obstructive pulmonary disease was admitted to medical intensive care unit with diagnosis of acute cholecystitis and acute renal failure from another healthcare facility. He had no history of coagulation disorder, and family history did not shown any bleeding condition. He had no underlying disorder or family history of hereditary coagulation disorder. He had been initiated on meropenem therapy for acute cholesistitis. He was on first day of meropenem and in septic shock on the admission day, and was taking noradrenaline. Blood and urine cultures were provided. Selected laboratory findings (and institutional normal ranges) were as follows: Serum creatinine level, 5.9 mg/dL (normal range 0.7-1.3 mg/dL); blood urea nitrogen 217 mg/dL (normal range 19-49 mg/dL); alanine aminotransferase (ALT), 340 U/L (normal range < 50 U/L); aspartate aminotransferase (AST), 309 U/L (normal range < 50 U/L); white blood cell count, 29.020 cells/mm$^3$ (normal range 3600-10500 cells/mm3); hemoglobin concentration, 15 g/dL (normal range 12.5-17.2 g/dL); platelet count 108×10$^9$ /L (normal range 160-400×10$^9$ /L); INR, 1.37 (normal range 0.8-1.2). Liver enzymes of patient, C-reactive protein (CRP) 0.155 g/L (0-0.005 g/L) and fibrinogen level 8.7 g/L (1.7-4.2 g/L) were high, INR was slightly elevated on the admission day. Peripheral blood smear on the admission showed leukocytosis with neutrophilia and platelet count was consistent with counter. On the 7$^{th}$ day of meropenem, patient's acute phase reactant levels increased, his fever continued and tigecycline was added to the treatment (tigecycline dose: 100mg q24 h loading dose, 50mg q12 h maintenance dose) The coagulation parameters were within the normal range before tigecycline treatment. On the 14$^{th}$ day of tigecycline, patient's infection improved with a dropped temperature (36.2$^o$C), white blood cell count (9.200 cells/mm3), platelet count 130×10$^9$ /L, and CRP (0.0259 g/L). Erythrocyte morphology was normal in the peripheral smear and platelet count was consistent with 150×10$^9$ /L.

Nevertheless, prolonged prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT) were observed; furthermore, fibrinogen levels were obviously decreased (Table 1). Liver failure findings were not observed, and the abdominal ultrasound was normal. As the patient's clinical signs of infection recovery, peripheral smear or other laboratory tests did not support disseminated intravascular coagulation, at that point we did not consider low fibrinogen, aPTT and PT elongation associated with disseminated intravascular coagulation. On that day tigecycline treatment was discontinued, meropenem was continued. After cessation of tigecycline, on the fifth day fibrinogen level became within the normal ranges and other

**Table1. Laboratory parameters of patient according to time course of antimicrobial therapy**

| | Fibrinogen (g/L) | aPTT (s) | PT (s) | INR | AST (U/L) | ALT (U/L) | Total bilirubin (mg/dL) | CRP (g/L) |
|---|---|---|---|---|---|---|---|---|
| **ICU admission** | 8.7 | 32.6 | 16.7 | 1.4 | 184 | 143 | 2.2 | 0.155 |
| **Tigecycline started** | 4.16 | 23.3 | 14.6 | 1.2 | 55 | 9 | 1.8 | 0.0564 |
| **5th day of tigecycline** | 2.04 | 30.7 | 16.3 | 1.4 | 19 | 7 | 1.9 | 0.0815 |
| **14th day of tigecycline** | 0.96 | 38.9 | 18.5 | 1.6 | 28 | 16 | 1.9 | 0.0259 |
| **5th day after tigecycline cessation** | 2.91 | 24.2 | 14.7 | 1.2 | 37 | 28 | 1.7 | 0.0731 |
| **10th day after tigecycline cessation** | 3.18 | 24.6 | 12.9 | 1.1 | 52 | 79 | 0.9 | 0.060 |

aPTT = activated partial thromboplastin time, PT = prothrombin time, INR = international normalized ratio, AST = aspartate aminotransferase, ALT = alanin aminotransferase, CRP = C-reactive protein, ICU = intensive care unit

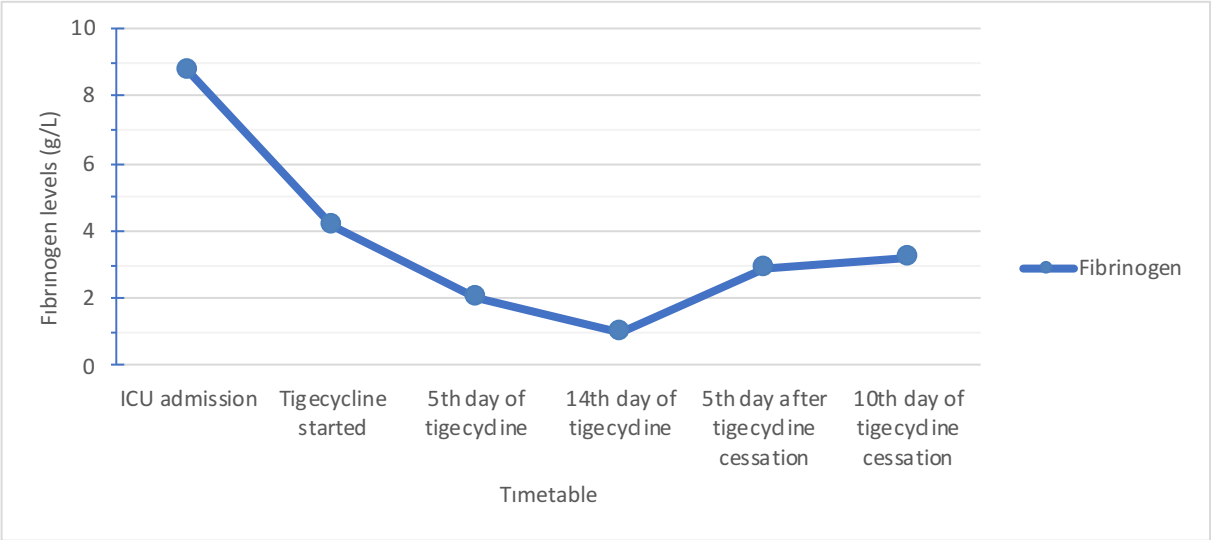


**Fig. 1. Fibrinogen levels of patient according to time course of antimicrobial therapy**

coagulation parameters became normal (Fig. 1). On the 67th day of ICU admission, patient was transferred to ward and after than discharged from ward.

## DISCUSSION

Tigecycline is a broad spectrum antibiotic, which is generally used for infections due to multidrug-resistant (MDR) bacteria [2]. It requires intravenous administration with a loading dose of 100 mg followed by a maintenance dose 50 mg every 12 hours. No dose adjustment is needed in patients with renal impairment, but only in patients with severe hepatic disfunction (Child-Pugh class C), the dosage should be reduced to 25 mg every 12 hours [1, 3]. Adverse reactions, in terms of haematologic and lymphatic system, as increased partial tromboplastin time, increased PT, increased INR, eosinophilia, and trombocytopenia, might be observed during usage was stated in the instructions of tigecycline [4]. But hypofibrinogenemia was not referred and a new adverse reaction. Life threatening coagulopathy and hypofibrinogenemia cases, induced by tigecycline use, were reported in the literature, by Wu and Wu [1], Wu *et al*. [3], Routsi *et al*. [6], Sabanis *et al*. [7], Pieringer *et al*. [8], Rossito *et al*. [9], and Yılmaz Duran *et al*. [10] (Table 2).

A few clinical studies reported hypofibrinogenemia and other coagulation abnormalities caused by tigecycline use [5, 6]. Our patient received routine dose, but in the literature some cases, which developed hypofibrinogenemia had received off-label higher doses of tigecycline [3, 6]. The mechanism in which tigecycline induced coagulopathy and caused hypofibrinogenemia, is unknown. Fibrinogen is produced by hepatocytes. It could be converted to insoluble fibrin to form blood clots, when trauma or sepsis occurs [1]. Effects of vitamin K deficiency on gut flora and inflammation due to serious infections are also commonly cited mechanisms resulting in coagulopathy. However, vitamin K replacement is reported not to improve coagulopathy, which is caused by tigecycline use [2]. In our case, serious infection might be thought to cause hypofibrinogenemia, but patient's infection parameters improved when fibrinogen level started to decrease. Furthermore, effect of tigecycline on liver functions could implicate decreased levels of fibrinogen [7]. Therefore, the underlying mechanisms of coagulopathy and hypofibrinogenemia and risk factors for these adverse effects should be elucidated. Also we suggest, regular monitoring of coagulation parameters, including fibrinogen level in patients receiving tigecycline. If patients develop hypofibrinogenemia, discontinuation of drug should be considered.

## CONCLUSION

We presented a patient who developed hypofibrinogenemia because of tigecycline use. The underlying mechanisms of coagulopathy and hypofibrinogenemia and risk factors for these adverse

**Table 2.** **Previous case reports and clinical studies about hypofibrinogenemia because of tigecycline use**

| References | Country | Study Type | Sex | Age | Admission Diagnosis | Renal/Liver Disease | TGC dose | Time of hypofibrinogenemia | Prognosis (days after TGC cessation) |
|---|---|---|---|---|---|---|---|---|---|
| Pieringer et al. [8] | Austria | Case report | F | 54 | Peritonitis | CRD | NM | Day 5 | Within 6 days |
| Rossito et al.[9] | Italy | Case report | F | 43 | Acute kidney injury | CRD+ Liver cirrhosis | 100mg loading dose 25 mg twice daily | Day 5 | Within 1 day |
| Sabanis et al.[7] | Greece | Case report | F | 74 | Prosthetic joint infection | CRD | 100 mg loading dose, 50 mg twice daily | Day 5 | Within 4 days |
| Routsi et al.[6] | Greece | Retrospective study | 31 M 14 F | 48 ± 20 | 20 severe sepsis 25 septic shock | NM | 100mg loading dose 6 patients 75mg teice Daily 39 patients 100mg twice daily | Day 1 | Within 10 days |
| Yılmaz Duran et al.[10] | Turkey | Case report | F | 90 | Pneumonia | CRD | NM | Day 10 | Within 8 days |
| Wu X et al. [3] | China | Case report | M | 47 | Acute cholangitis | No | 100mg loading dose, 100mg twice daily | Day 2 | Within 5 days |
| Wu and Wu [1] | China | Case report | M | 87 | Pneumonia | CRD | 100mg loading dose 50 mg twice daily | Day 7 | Within 5 days |
| Zhang et al.[4] | China | Retrospective control | 16 M 4 F | 62.5 ± 22.1 | 4 intraabdominal 1 skin and soft tissue 4 bacteremia 11 pneumoniae | 4 patients CRD 4 patients CHD | | NM | NM |

F = female, M = male, CRD = chronic renal disease, CHD = chronic hepatic disease, NM =not mentioned, TGC = Tigecycline

effects should be elucidated. We suggest, regular monitoring of coagulation parameters including fibrinogen level in patients receiving tigecycline. If patients develop hypofibrinogenemia, discontinuation of drug should be considered.

*Authors' Contribution*

Study Conception: HRG, MA, SK, FC; Study Design: RG, MA, SK, FC; Supervision: RG, MA, SK, FC; Fundings: MA; Materials: MA, SK, FC; Data Collection and/or Processing: MA; Statistical Analysis and/or Data Interpretation: MA, RG; Literature Review: MA; Manuscript Preparation: MA and Critical Review: MA, RG.

*Informed consent*

Written informed consent was obtained from the patient for publication of this case and any accompanying images.

*Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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