RESEARCH ARTICLE

Journal of Anatolian Medical Research
JAMER 2024;9(3):88-92
DOI: 10.55694/jamer.1478894

Evaluation of the Prognostic Value of Inflammatory Biomarkers in Immunoglobulin A Nephropathy

İmmünoglobulin A Nefropatisinde İnflamatuvar Biyobelirteçlerin Prognostik Öneminin Değerlendirilmesi

Hakan Saraçoğlu[1], Bülent Tokgöz[2], İsmail Koçyiğit[2]

[1] Kayseri City Hospital, Department of Internal Medicine, Kayseri, Türkiye
[2] Erciyes University, Faculty of Medicine, Department of Nephrology, Kayseri, Türkiye

ABSTRACT

Aim: *Immunoglobulin A (IgA) nephropathy, the most prevalent primary glomerulonephritis, carries the potential for progression to kidney failure. The researches are going on for biomarkers that can be used to predict the prognosis. This study aimed to evaluate the effect of some inflammatory parameters on prognosis in IgA nephropathy.*

Materials and Methods: *The study included 53 patients diagnosed with IgA nephropathy. Blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR), urinary microprotein/creatinine (Mp/Cr) ratio, white blood cell count (WBC), mean platelet volume (MPV), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), erythrocyte sedimentation rate (ESR), and C-Reactive protein (CRP) at initial admission, along with eGFR values at subsequent follow-ups (1, 3, and 5 years), were retrospectively analyzed. Poor prognosis was defined as a 50% or greater reduction in eGFR, hemodialysis requirement, kidney transplantation, or exitus.*

Results: *Patients with poor prognosis exhibited higher BUN, creatinine, and Mp/Cr ratio, accompanied by lower eGFR levels. Notably, among the inflammatory biomarkers, only MPV demonstrated a significant difference between the prognosis groups, with lower values observed in the poor prognosis group (p=0.006). ROC analysis revealed significant predictive value for all five parameters (BUN, creatinine, eGFR, urine Mp/Cr and MPV), with MPV showing the highest AUC value (0.78).*

Conclusion: *This study pioneers the evaluation of MPV as a prognostic marker in IgA nephropathy. Pending confirmation through subsequent investigations, MPV holds promise as a valuable prognostic indicator for IgA nephropathy.*

Keywords: *Immunoglobulin A nephropathy, inflammatory biomarker, mean platelet volume, prognosis*

ÖZET

Amaç: *En yaygın primer glomerülonefrit olarak bilinen immünoglobulin A (IgA) nefropatisi, böbrek yetmezliğine ilerleme potansiyeli taşımaktadır. Prognozu tahmin etmek için kullanılabilecek biyobelirteçler için araştırmalar devam etmektedir. Bu çalışmanın amacı, IgA nefropatisinde bazı inflamatuar parametrelerin prognoz üzerine etkisini değerlendirmektir.*

Gereç ve Yöntemler: *Çalışmaya IgA nefropatisi tanısı konulan 53 hasta dahil edildi. İlk başvurudaki kan üre azotu (BUN), kreatinin, tahmini glomerüler filtrasyon hızı (eGFR), idrar mikroprotein/kreatinin (Mp/Cr) oranı, beyaz kan hücresi sayısı (WBC), nötrofil/lenfosit oranı (NLR), trombosit/lenfosit oranı (PLR), ortalama trombosit hacmi (MPV), eritrosit sedimantasyon hızı (ESR) ve C-reaktif protein (CRP) ile birlikte, bir, üç ve beşinci yıl kontrollerindeki eGFR değerleri retrospektif olarak değerlendirildi. Herhangi bir kontrolde eGFR'de %50 veya daha fazla azalma olması, hemodiyaliz gereksinimi, böbrek transplantasyonu veya eksitus kötü prognoz olarak kabul edildi.*

Bulgular: *Kötü prognostik grup, iyi prognostic gruba göre daha yüksek BUN, kreatinin ve Mp/Cr oranları ile birlikte, daha düşük eGFR düzeylerine sahipti. İnflamatuvar biyobelirteçlerden ise sadece MPV prognoz grupları arasında anlamlı bir fark gösterdi ve kötü prognostik grupda daha düşük değerler gözlendi (p=0.006). ROC analizi, iki grup arasında anlamlı farklı bulunan beş parametrenin (BUN, kreatinin, eGFR, idrar Mp/Cr ve MPV) anlamlı öngörücü değere sahip olduğunu gösterirken, MPV en yüksek AUC değerine (0,78) sahipti.*

Sonuç: *Bu çalışma, MPV'nin IgA nefropatisinde prognostik bir belirteç olarak değerlendirilmesine öncülük etmektedir. Sonraki araştırmalarla doğrulanmayı bekleyen MPV, IgA nefropatisi için değerli bir prognostik gösterge olarak umut vaat etmektedir.*

Anahtar Kelimeler: *Immünoglobulin A nefropatisi, inflamatuar belirteç, prognoz, ortalama platelet hacmi*

Corresponding Author: Hakan Saraçoğlu, Kayseri City Hospital, Department of Internal Medicine, Kayseri, Türkiye ***Email:*** drhakansaracoglu@gmail.com
Cite this article as: Saraçoğlu H, Tokgöz B, Koçyiğit İ. Evaluation of the Prognostic Value of Inflammatory Biomarkers in Immunoglobulin A Nephropathy. JAMER 2024;9(3):88-92.

Received: 01.04.2024
Accepted: 13.11.2024
Online Published: 31.12.2024

INTRODUCTION

IgA nephropathy (IgAN) is a clinicopathological syndrome characterized by deposition of IgA in the glomerular mesangium, mesangial cell proliferation, and recurrent episodes of hematuria. It is the most prevalent primary glomerular disease (1). Patients may present with a spectrum of signs and symptoms, ranging from asymptomatic microscopic hematuria to kidney function impairment (2,3). Despite the researches on many immunosuppression agents maintain, there is no specific treatment exists for IgAN. Currently the essential of the IgAN treatment is supporting kidney care, such as blood pressure controlling, salt-free diet, angiotensin blockage, and endothelin antagonism (4). The prognosis of IgAN is highly variable. Approximately 20-30 years after the initial clinical presentation, 30-40% of patients may develop end-stage kidney disease. Diagnostic findings indicative of disease progression include high serum creatinine, hypertension (>140/90 mm-Hg), and persistent proteinuria exceeding 1 g/day for more than six months (5).

IgAN is a complex disease influenced by various factors affecting its development and prognosis. Although its pathogenesis remains incompletely elucidated, autoimmunity and inflammation are thought to be the primary mechanisms (6,7). The widely accepted "four hits" hypothesis outlines the key steps in disease progression: (1) increased insufficient galactosylated IgA1 in plasma; (2) development of autoantibodies against insufficient galactosylated IgA1; (3) formation of immune complexes; (4) mesangial deposition complexes leading to disruption of glomerular functions through activation of mesangial cells. Consequently, cells and molecules of the immune system participate in the pathogenesis of IgAN through diverse mechanisms (8). This complexity suggests that inflammatory parameters may serve as potential biomarkers to predict prognosis in IgAN.

In the current study, we have purposed to assess the utility of specific inflammatory biomarkers and inflammation-related hemogram parameters in predicting IgAN progression.

MATERIALS and METHODS

This study was conducted as single-center and the data collection was based on retrospective analysis. Patients screening was performed in the Erciyes University Nephrology Department for last 10 years. Only patients with biopsy proven IgAN diagnosis and having an estimated glomerular filtration rate (eGFR) above 30 ml/min/1.73m^2 were included. Patients who were not maintained follow-up regularly were excluded due to insufficient medical data. Additionally, patients with known active infections during the kidney biopsy period were excluded, as infections could alter inflammatory markers. Exclusion criteria were clinical signs of active infection, such as fever, a CRP level >20 mg/L, a white blood cell count >12,000/uL, and the absolute neutrophil count >6,000/uL.

The following data were recorded at first admission: the presence of diabetes mellitus (DM) and/or hypertension (HT), crescent formation in kidney biopsy, systolic and diastolic blood pressure (BP), blood urea nitrogen (BUN), creatinine, eGFR, (calculated by the Chronic Kidney Disease-Epidemiology Collaboration, CKD-EPI formula), urinary protein to creatinine ratio (uPCR), erythrocyte sedimentation rate (ESR), CRP, white blood cell (WBC), neutrophil, lymphocyte, platelet counts, and mean platet volume (MPV). By usinng their formulas: NLR= neutrophil count/lymphocyte count, PLR=platelet count/ lymphocyte count.

Additionally, eGFR values at the first, third, and fifth-year follow-ups were screened, and eGFR change % values were calculated using the following formula:
eGFR change% = [(eGFRfirst admission - eGFRcontrol) / eGFRfirst admission)] x 100

The patients were then categorized into two groups for analysis: 1) good prognosis group and 2) poor prognosis group. Based on the criteria defined by the SPRINT study group (9), if a patient has above 50% reduction in eGFR, or kidney replacement requirement, or death was defined as poor prognosis. Finally, two progression groups were compared according to recorded data.

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki and received approval from the Erciyes University Clinical Research Ethical Committee (decision no: 2020/52, date: 29/01/2020).

Statistics

Statistical Analysis was conducted using SPSS Statistics 25 software (IBM Corporate, Armonk, New York). Summary statistics of continuous variables and categorical variables were presented as mean±standard deviation (X ± SD) or frequency and %, respectively. Independent samples t-test and chi-square analysis were performed for comparisons between the two groups. Receiver-Operating Characteristic (ROC) analysis was employed to determine the cut-off, sensitivity, specificity, and the area under the curve (AUC) values of variables associated with poor prognosis. p values below 0.05 considered statistically significant.

RESULTS

This study included a total of 53 patients. The mean age

of the patients was 38.5 ± 13.2 years. The group consisted of 33 males (62.3%) and 20 females (37.7%). The average initial eGFR level was 70.3±32.9 mL/min/1.73m^2. The average initial uPCR level was 2.0±1.4 mL/min/1.73m^2. Poor prognosis was determined in 20 (37.7%) patients. eGFR reduction more than 50% was determined in two patients, dialysis treatment was determined in six patients; kidney transplantation was determined in seven patients, and death was in five patients. The remaining 33 (62.3%) patients were categorized into the good prognosis group.
Firstly, the two IgAN progression groups were compared according to clinical and demographic features. Age and gender did not demonstrated statistically significant different distribution between two IgAN progression groups. The frequency of DM was statistically significantly different between two groups. The frequency of HT was statistically significantly higher (p=0.014) in the poor prognosis group (33.3%) when compared with good prognosis group (8.0%). These results were summarized in Table 1.

Table 1. Demographic and clinical characteristics of the prognosis groups

		Good Prognosis (n=33)	Poor Prognosis (n=20)	p
Age		37.2±14.3	40.5±11.2	0.383
Gender (Male)		20 (60.6%)	13 (65.0%)	0.549
Diabetes Mellitus	Yes	4 (12.1%)	2 (10.0%)	0.513
	No	29 (87.9%)	18 (90.0%)	
Hypertension	Yes	2 (8.0%)	5 (33.3%)	**0.014**
	No	23 (92.0%)	10 (66.7%)	
Crescent Formation		8 (24.2%)	3 (15.0%)	0.421
Systolic BP (mm-Hg)		121.61±13.95	127.5±17.22	0.223
Diastolic BP (mm-Hg)		77.14±9.76	76.25±8.06	0.758

BP: *Blood pressure*

The two IgAN progression groups were compared according to initial kidney function tests. In patients with poor prognosis group statistically significant lower (p=0.003) eGFR levels were seen when compared with patients with good prognosis. The initial eGFR was 80.6±30.0 mL/min/1.73m^2 in patients with good prognosis and 53.2±30.9 mL/min/1.73m^2 in patients with poor prognosis. Furthermore, In patients with a poor prognosis statistically significantly higher (p=0.012) uPCR levels were seen when compared patients with good prognosis. The initial uPCR level was 1.6±1.1 mg/mg in patients with good prognosis and 2.7±1.6 mg/mg in patients with a poor prognosis. The results were summarized in Table 2.

There were no statistically significant differences in specific inflammatory biomarkers (ESR and CRP) and inflammation-related hemogram parameters (WBC, neutrophil, lymphocyte, platelet, NLR, PLR) between two IgAN progression groups. Only MPV was statically significantly lower (p=0.006) in patients with a poor prognosis. The results were summarized in Table 2. MPV was 8.9±1.1 fL in patients with good prognosis and 8.0±1.1 fL in patients the poor prognosis (Figure 1).

Table 2. Biochemical parameters of prognosis groups

	Good Prognosis (n= 33)	Poor Prognosis (n=20)	*p*
eGFR (ml/min/1.73m^2)	80.68±30.07	53.28±30.95	**0.003**
uPCR	1.68±1.13	2.69±1.68	**0.012**
WBC (10^3/µL)	8.63±2.39	7.83±1.86	0.205
Neutrophil (10^3/µL)	5.28±2.33	4.91±1.27	0.515
Lymphocyte (10^3/µL)	2.23± 0.88	1.93± 0.85	0.223
Platelet (10^3/µL)	246±54	218±75	0.120
MPV (fL)	8.96±1.16	8.01±1.19	**0.006**
NLR	2.76±1.73	3.14±1.99	0.474
PLR	123.01±46.55	135.66±72.82	0.443
ESR (mm/h)	20.93±20.76	28.23±20.02	0.299
CRP (mg/L)	7.83±7.47	8.65±10.43	0.779

eGFR: *estimated glomerular filtration rate,* ***uPCR:*** *urinary protein to creatinine ratio,* ***WBC:*** *White blood cell,* ***MPV:*** *mean platelet volume,* ***NLR:*** *neutrophil to lymphocyte ratio,* ***PLR:*** *platelet to lymphocyte ratio,* ***ESR:*** *erythrocyte sedimentation rate. Statistical significance is indicated in bold*

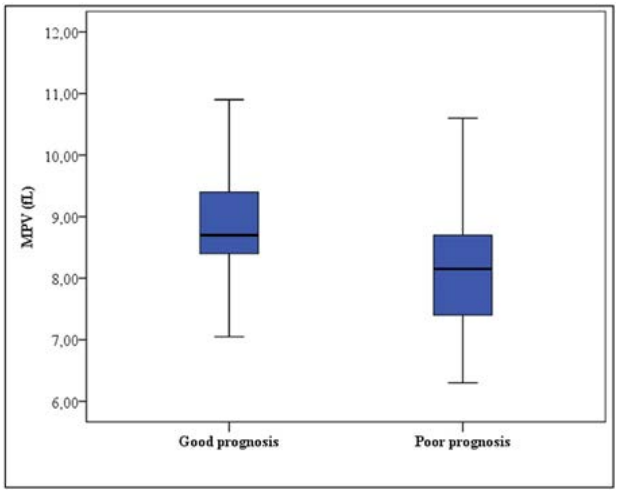

Figure 1. Comparative box-plot graphic of MPV between prognosis groups.

ROC analysis was performed to evaluate the diagnostic performance of parameters predicting poor prognosis of IgAN. All five parameters (BUN, creatinine, eGFR, uPCR, and MPV) had significant predictive values. The results were summarized in Table 3 and demonstrated in Figure 2. While the AUC values were closely aligned, MPV demonstrated the highest AUC (0.78) the ROC analysis.

DISCUSSION

We conducted a retrospective evaluation of the prognostic predictivity of various inflammatory markers as well

as certain clinical and biochemical parameters, which had previously been recognized for their prognostic significance in IgAN.

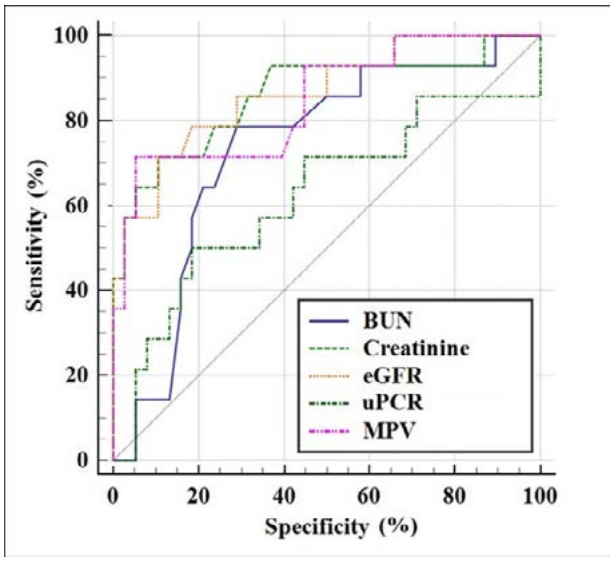

Figure 2. Comparison of ROC curve of biochemical parameters.

Table 3. Performance data of biochemical parameters in ROC analysis

	Cut-off	Sensitivity%	Specificity%	AUC	p
BUN	13.25	78	75	0.77	**<0.001**
Creatinine	0.765	77	79	0.74	**0.004**
eGFR	26.75	71	81	0.77	**0.001**
MPV	6.925	79	72	0.78	**0.001**
uPCR	0.89	71	75	0.74	**0.002**

AUC: *area under the curve,* ***BUN:*** *blood urea nitrogen,* ***eGFR:*** *estimated glomerular filtration rate,* ***MPV:*** *mean platelet volume,* ***uPCR:*** *urinary protein to creatinine ratio.*

Statistical significance is indicated in bold.

The most important outcome of this study was related to MPV, which serves as an inflammatory marker, was significantly lower in patients with poor prognosis group when compared to the patients with good prognosis. Furthermore, ROC analysis revealed with a MPV may be a valuable biomarker in predicting poor prognosis of IgAN. During an inflammatory condition, the intracellular synthesis of procoagulant and proinflammatory factors causes an increase in the percentage of large platelets (increase in MPV), possibly due to degranulation and release of the platelet pool in the spleen. At the same time, these cells rapidly migrate to the site of inflammation. This explains the low MPV in the chronic inflammation (10). Therefore, MPV could reflect systemic inflammation status. Based on this mechanism, lower MPV values in poor prognosis than in good prognosis may be due to a longer-term and / or more severe inflammation.

Prior studies have highlighted the diagnostic and prognostic significance of MPV in various diseases. Yun et al. revealed that MPV was reduced in 19.9% of renal cell carcinoma patients, correlating with shorter survival times. Decreased MPV emerged as an independent prognostic factor for overall survival (11). Nainggolan et al. explored MPV variations in active and remission phases of children with nephrotic syndrome, noting lower MPV values during the active period (12). In systemic lupus erythematosus (SLE), MPV was observed to be lower during activation compared to remission (13,14). A notable decrease in MPV was also observed during active periods of ulcerative colitis and Crohn's disease (15,16). However, we did not encounter any studies evaluating MPV levels in IgAN in the literature review, accordingly, the current study stands as the first.

While certain reports have highlighted the prognostic relevance of other inflammatory markers like WBC, neutrophils, NLR, and PLR. For example, Li et al. reported that NLR levels were elevated in patients with IgAN when compared to healthy controls, and the easily available NLR in clinical practice could serve as an independent risk factor for IgAN progression (17-19). However, none of these inflammatory biomarkers levels shown significant differences between the two IgAN prognosis groups in our study. This discrepancy may be attributed to the relatively small sample size of our study compared to existing literature and/or the exclusion of patients with active infection at the time of admission, a factor not consistently considered in similar studies (not specified as exclusion criteria).

Prior studies have highlighted the prognostic importance of HT or significant elevation in blood pressure at the time of diagnosis (5). In our investigation, the incidence of HT was notably higher (33.3%) in the poor prognosis group, establishing HT as an independent risk factor. However, there was no discernible difference in systolic/diastolic blood pressures at the time of diagnosis between the groups. This may be related to the control of blood pressure with antihypertensive medications before the study, such as renin-angiotensin system (RAS) bloker.

Decreased initial eGFR, as evidenced by increased serum creatinine, has been consistently associated with an unfavorable kidney outcomes. A substantial prospective study demonstrated a cumulative incidence of kidney failure linked to high serum creatinine and low GFR levels at diagnosis (20). Likewise, another study in patients with stage 3-5 chronic kidney disease revealed an association between high BUN levels and poor kidney outcomes (21). In line with these findings, our study identified higher

BUN and creatinine levels and lower eGFR levels in the poor prognosis group. The prognostic performances of BUN and creatinine were comparable, with eGFR emerging as the most specific parameter for predicting poor prognosis. Our analysis revealed an elevated uPCR levels in the poor prognosis group at IgAN diagnosis. This aligns with previous research emphasizing proteinuria as a crucial prognostic marker in IgA nephropathy (4,5,22).

Conclusion

Our study sheds light on the predictive roles of initial inflammatory markers in IgAN progression. We identified initial eGFR, uPCR, and MPV as differentiating factors between two prognosis groups. Our investigation is the first to evaluate the prognostic predictivity of MPV in IgAN and demonstrated that lower MPV level is associated with poor kidney outcomes. These findings provide a preliminary basis for further studies, suggesting the potential of MPV level as a promising prognostic marker in IgAN.

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and received approval from the Erciyes University Ethical Committee (decision no: 2020/52, date: 29/01/2020).
Conflict of Interest: None declared.
Financial Disclosure: No financial support was received from any institution or organization for this study.
Author Contributions: Concept – BT, IK; Design – BT, IK; Supervision – BT, IK; Resources – HS; Materials – HS; Data Collection and/or Processing – HS; Analysis and/or Interpretation – HS; Literature Search – BT, IK, HS; Writing Manuscript – HS, BT, IK; Critical Review – BT, IK

REFERENCES

1. Peker BO, Müderris T, Yurtsever SG, Kaya S. Servikal fırça örneklerinde insan papilloma virüs prevalansı ve genotip dağılımı; üç yıllık analiz. Turk Mikrobiyol Cemiy Derg. 2022;52(3):168-174.
2. Nikolic N, Basica B, Strbac M, Terzic L, Patic A, Kovacevic G, et al. Prevalence of Carcinogenic Genotypes of HPV-Infected Women in a Ten-Year Period (2014-2023) in Vojvodina, Serbia. Medicina (Kaunas). 2024;60(6):922.
3. Gultekin M, Kucukyildiz I, Karaca MZ, Dundar S, Boztas G, Turan SH, et al. Trends of gynecological cancers in Turkey: Toward europe or asia? International Journal of Gynecologic Cancer. 2017;27:1-9.
4. Koç Ö, Baltacı N, Yüksekol ÖD. Kadınların serviks kanseri taraması inançlarının Hpv aşısına yönelik inançları ile ilişkisi. Turkish Journal of Family Medicine and Primary Care. 2023;17(1):31-41.
5. Ozan H, Demir BÇ, Atik Y, Gümüş E, Özerkan K. Kadın hastalıkları ve doğum polikliniğine başvuran hastaların human papilloma virüs ve HPV aşısı hakkındaki bilgi düzeylerinin belirlenmesi.Uludağ Üniversitesi Tıp Fakültesi Dergisi. 2011;37(3):145-148.
6. Yöntem M, Gümüş A, Abalı R, Öznur M, Erci F, Erdoğdu BS. Human papilloma virüs (HPV) varlığının cinsel aktif kadınlarda moleküler metodlarla değerlendirilmesi. Academic Platform-Journal of Engineering and Science. 2019;7(2): 217-221.
7. Siegler E, Reichman Y, Kugelman N, Mackuli L, Lavie O, Ostrovsky L, et al. Low-risk human papillomavirus types in cervical intraepithelial neoplasia 2–3 and in invasive cervical cancer patients. Journal of Lower Genital Tract Disease. 2019;23(4): 248-252.
8. Böyük M, Bilgin NÇ. HPV enfeksiyonuna güncel bir bakış: nedenleri, etkileri ve korunma. Abant Sağlık Bilimleri ve Teknolojileri Dergisi. 2023;3(1): 40-47.
9. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2021;71(3): 209-249.
10. Akalın A. Human Papillomavirus (HPV) Enfeksiyonu ve HPV aşısında güncel yaklaşımlar. Androl Bul. 2022;24:133-139.
11. Böyük M, Çıtak Bilgin N. HPV enfeksiyonuna güncel bir bakış: Nedenleri, etkileri ve korunma. SABİTED. 2023;3(1):40-47.
12. WHO. Comprehensive Cervical Cancer Control: A guide to essential practice. Geneva: 2014.
13. Bayram A, Karaca Derici Y, Ozkalay Yilmaz N, Yilmaz Hanci S, Agus N, Sirin MC, et al. Prevalence of high-risk human papillomavirus in women from Turkey. Clin Obstet Gynecol Reprod Med. 2015;1(3):84-86.
14. Mosmann JP, Zayas S, Kiguen AX, Venezuela RF, Rosato O, Cuffini CG. Human papillomavirus and chlamydia trachomatis in oral and genital mucosa of women with normal and abnormal cervical cytology. BMC Infect Dis. 2021;21(1):422.
15. Jaworek H, Koudelakova V, Drabek J, Vrbkova J, Zborilova B, Oborna I, et al. A head-to-head analytical comparison of cobas 4800 HPV, papilloCheck HPV screening, and LMNX genotyping kit HPV GP for detection of human papillomavirus DNA in cervical and cervicovaginal swabs. J Mol Diagn. 2018;20(6):49-58.
16. Smolarz B, Samulak D, Szyłło K, Romanowicz MMH, Kojs Z, Michalska MM. Cobas 4800 HPV detection in cervical samples of polish women. Contemp Oncol (Pozn). 2019; 23(2): 92-95.
17. Wang S, He X, Meng F, Pan Q, Zhang L, Zeng J. Application of the cobas 4800 system for the detection of high-risk human papillomavirus in 5650 asymptomatic women. Biomed Res Int. 2020;2020:1635324.
18. Aydemir Ö, Terzi HA, Köroğlu M, Turan G, Altındiş M, Karakeçe E. Servikal örneklerde HPV-DNA pozitiflik oranı ve sitopatolojik sonuçların değerlendirilmesi. Turk Hij Den Biyol Derg. 2020;77(1):33-40.
19. Erickson BK, Alvarez RD, Huh WK. Human papillomavirus: what every provider should know. American journal of obstetrics and gynecology. 2013;208(3):169-175.
20. Dursun P, Ayhan A, Mutlu L, Çağlar M, Haberal A, Güngör T, et al. HPV types in Turkey: Multicenter hospital based evaluation of 6388 patients in Turkish gynecologic oncology group centers. Turk Patoloji Derg. 2013;29: 210-216.
21. Aydoğan S, Yazgan A, Taş EE, Gözalan A, Yavuz AF, Açikgöz ZC. The presence and distribution of high risk HPV types in simultaneous cervical cytology samples. Turk Hij Den Biyol Derg. 2018;75(1):13-20.
22. Gultekin M, Zayifoglu Karaca M, Kucukyildiz I, Dundar S, Boztas G, Semra Turan H, et al. Initial results of population based cervical cancer screening program using HPV testing in one million Turkish women. International journal of cancer. 2018;142(9):1952-1958.