IZMIR DEMOCRACY UNIVERSITY HEALTH SCIENCES JOURNAL
IDUHES
e-ISNN:2651-4575

IDUHeS, 2023; 6(2): 337-347
Doi: 10.52538/iduhes.1277754

Research Paper – Araştırma Makalesi

IRON DEFICIENCY ANEMIA IN CANCER PATIENTS IN PALLIATIVE CARE

PALYATİF BAKIMDA KANSERLİ HASTALARDA DEMİR EKSİKLİĞİ ANEMİSİ

Orkun SARICAM[1], Gulhan SARICAM[2]

Özet

Bu çalışmada amacımız, kanserli hastaların anemi derecesi ile metastaz, performans, beslenme durumu gibi etkenleri karşılaştırarak prognoza etkisini araştırmaktır. Bu retrospektif çalışmaya palyatif bakımda (PB) izlenen kanserli 189 hasta dahil edildi. Hastalar kanser tanılarına göre sınıflandırıldı, demografik özellikleri, anemi paneli, kemoterapi, metastaz, performans durumu, yatış süreleri ve çıkış durumları kayıt edilerek gruplar arasında karşılaştırıldı. PB'da izlediğimiz kanserli hastaların %85.7'sinde anemi ve %88,4' ünde metastaz vardı. Anemisi şiddetli olanlarda, Eastern Cooperative Oncology Group Scale (ECOG) skoru anemisi olmayanlardan ve C-reaktif protein (CRP) düzeyleri diğer gruplardan anlamlı derecede yüksek bulundu. (p=0,045, p=0,000). Orta derecede anemisi olanlarda Glaskow Koma Skalaları (GKS), anemisi olmayanlardan anlamlı derecede daha düşük bulundu (p=0,049). PB'da izlediğimiz ileri evre kanserli hastalarda, düşük GKS, düşük performans ve yüksek CRP değerleri gibi kötü prognostik kriterler ile anemi şiddetinin ilişkili olabileceğini gösterdik. Kanser hastalarında hastalığın seyri sırasında aneminin erken değerlendirilmesi ve yeterli besin alımı sağlanmalı ve bu tür müdahalelerin sağkalım ve prognoz üzerine etkileri geniş çaplı çalışmalarla araştırılmalıdır.

Anahtar Kelimeler: Anemi, kanser, palyatif bakım

Abstract

In this study, we aimed to investigate the effects of anemia on the prognosis by comparing the severity of anemia with several prognostic factors including metastases, functional performance, and the feeding status of cancer patients. This retrospective study included 189 cancer patients, who received treatment in the palliative care unit (PCU). Demographic characteristics of the patients, anemia test panel results, chemotherapy, the status of metastases, functional performance, the length of hospital stay, and the status at discharge were recorded and compared between the study groups. Of the cancer patients in PCU, 85.7% had anemia and 88.4% had metastases. In patients with severe anemia, the Eastern Cooperative Oncology Group Scale (ECOG) scores higher than without anemia and C-reactive protein (CRP) levels were significantly higher compared to the other patients in other groups (p=0.045, p=0.000). Glasgow Coma Scales (GCS) were found to be significantly lower in patients with moderate anemia than those without anemia. (p=0.049) We have shown that there may be an association between the severity of anemia and poor prognostic criteria including low GCS scores, poor performance and high CRP levels in advanced cancer patients we treated in PCU. Early assessment of anemia and the adequate intake of nutrients should be ensured in cancer patients during the disease course and its effects of such interventions on survival and prognosis should be investigated through large-scale studies.

Keywords: Anemia, cancer, palliative care

Geliş Tarihi (Received Date): 05.04.2023, Kabul Tarihi (Accepted Date): 26.05.2023, Basım Tarihi (Published Date): 30.09.2023. [1] Ankara Pursaklar State Hospital, Department of Internal Medicine, Ankara, Türkiye, [2] Ankara Pursaklar State Hospital, Department of Neurology Clinic, Ankara, Türkiye, [3] **E-mail:** orkunsar@hotmail.com **ORCID ID's:** O.S.; https:/orcid.org/0000-0001-5820-0951, G.S.; https:/orcid.org/0000-0002-9032-6877.

1. INTRODUCTION

Anemia in cancer patients is a common complication with unfavorable functional and physical effects along with adverse consequences on the quality of life, survival, and prognosis. Anemia in cancer patients often results from chronic blood loss, chronic inflammation, treatment-induced myelosuppression, the tumoral infiltration of the bone marrow, and impaired iron homeostasis due to dietary deficiencies (Clarke et al., 2005, pp.1-13; Birgegard et al., 2005, pp.3–11),

The management of commonly observed anemia in patients with advanced cancers has gained importance over the past decade in parallel with the increasing role of palliative care (PC) for addressing symptoms and treatment requirements in such patients (Neoh et al., 2022, pp.783–794). A study on PC patients suffering mostly from advanced cancers showed that 77% of men and 68.2% of women had anemia (Dunn et al., 2003, pp.1132–1139). Neoh et al. (2016, pp.1209–1214) showed that 38% of advanced cancer patients receiving PC were diagnosed with moderate or severe functional iron deficiency anemia. Iron deficiency was previously associated with deteriorations in the quality of life and physical performance in cancer patients and it has been suggested that especially the maintenance of adequate hemoglobin levels may improve survival (Ludwig et al., 2013, pp.1886–1892; Demetri et al., 1998, pp.3412-3425).

Despite the availability of studies about iron deficiency anemia in cancer patients in the literature, little is known about the prevalence and prognostic effects of anemia in cancer patients receiving PC. In this study, we categorized cancer patients receiving palliative care into solid and hematological malignancy groups to evaluate the prevalence of iron deficiency of anemia. We compared the severity of anemia with patients' metastasis status, functional performance, feeding status, status at the time of hospital discharge, and length of hospital stay (LOS) to explore the effects of such factors on prognosis.

2. METHODS

Ethics committee approval of the study was obtained from the Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (2021-124/05). All procedures were applied in accordance with the principles of the Declaration of Helsinki. The retrospective study included 189 patients who received treatment with the diagnosis of cancer in the palliative care unit (PCU) in the period between January 2017 and January 2022. Based on their diagnoses, patients were categorized into head and neck cancers, lung cancer, breast cancer, gastrointestinal system cancers, genitourinary system (GUS) + gynecological cancers, and hematologic cancers (leukemia, lymphoma, myeloma, etc.). All patients in the study had advanced cancers. Recorded patient data included age, gender, the presence of metastases, chemotherapy status, patient feeding methods (oral, percutaneous endoscopic gastrostomy – PEG-), Glasgow Coma Scale (GCS) scores, Eastern Cooperative Oncology Group Scale (ECOG) scores, status at the time of discharge (whether discharged to home or intensive care unit (ICU) or not survived), and the length of stay in PCU. In addition, the results from complete

blood counts and the levels of transferrin saturation, iron, ferritin, and C-reactive protein (CRP) were recorded.

Hemoglobin levels were examined according to the World Health Organization (WHO) criteria. Hemoglobin levels of <80 g/l were considered severe anemia and levels of 80-110 g/l were considered moderate anemia. Hemoglobin levels of 110-130 g/l in men and 110-120 g/l in women were considered mild anemia (WHO, 2011). The level of consciousness was evaluated with GCS. GCS is a scale to evaluate the consciousness of patients by assessing the verbal, motor, and eye-opening responses of patients. The best response is scored 15, while the worst response is scored 3 (Teasdale et al., 1974, pp.81-4). In the ECOG performance scale, a score of 0 denotes normal health status, while a score of 5 denotes the death of the patient. Low scores are the indicators of favorable general health status, but high scores predict poor prognosis (Oken et al., 1982, pp.649-655)

2.1. Statistical analysis

Study data were collected from 189 individuals. IBM SPSS Statistics 26 package software were used for analyzes. Categorical variables were described by numerical variables (numbers, percentages) and frequency were described by descriptive statistics (standard deviation and mean). Kolmogorov Smirnov test of normality was used for the normality assumptions of the numerical variables, and it was found that the variables were not normally distributed. Therefore, nonparametric statistical methods were used in the statistical analysis. Chi-square analyses were used for the relationships between two independent categorical variables. Differences across more than two independent groups were evaluated with the Kruskal-Wallis test. When differences were revealed by the Kruskal-Wallis analysis, Bonferroni corrected results were used to identify the group causing differences. A significance level of 0.05 was used to interpret the results.

3. RESULTS

The patients in the study had cancers. The mean age was 68.85±14.12 years and 58.2% of the patients were women. Of the patients, metastases were present in 88.4%, chemotherapy was administered to 81.5%, and ECOG scale scores of 4 were found in 76.2%. The mean GCS score was 10.71 ± 1.91. The mode of feeding was oral in 78,3% and through a PEG in 21.7% of the patients. Anemia was detected in 85.7% of the patients. Of the patients with anemia, the severity was moderate in 51.9%. Nonsurvivors accounted for 47.1% of the patients, while 40.7% of patients were discharged to home. The mean LOS was 20.33±15.07 days. (Table 1)

Table 1. Demographic characteristics of patients

	(n=189)	Number (%)
Gender		
Female		110 (58.2)
Male		79 (41.8)
Tumour Site		
Head/neck		30 (15.9)
Lung		31 (16.4)
Breast		41 (21.7)
Gastrointestinal		40 (21.2)
GU + Gyn		27 (14.3)
Hematological		20 (10.6)
Metastasis		
No		22 (11.6)
Yes		167 (88.4)
Chemotherapy		
No		35 (18.5)
Yes		154 (81.5)
ECOG		
3		45 (23.8)
4		144 (76.2)
Nutrition		
PEG		41 (21.7)
Oral		148 (78.3)
Anemia		
Not anemic		27 (14.3)
Mild		32 (16.9)
Moderate		98 (51.9)
Severe		32 (16.9)
Discharge Status		
Home		77 (40.7)
ICU		23 (12.2)
Exitus		89 (47.1)
		Mean±SD
Age		68.85±14.12
GCS		10.71±1.91
Haemoglobin (gr/dl)		101.65±20.81
MCV (fl)		87.34±11.05
Platelet ($\times 10^3$ µl)		268.58±128.48
Ferritin (mg/l)		27.14±38.55
Iron (ug/dl)		46.92±31.25
Transferrin S.(%)		14.76±10.77
CRP (mg/l)		11.00±12.32
LOS (Days)		20.33±15.07

The chi-square analysis revealed a statistically significant correlation of the diagnosis with gender, oral intake, and the use of PEG ($p<0.05$). A PEG was significantly more commonly found in patients with the cancers of the head and neck compared to the cancers of the breast and GIS. ($p=0.000$) Oral intake was significantly more common among patients with the cancers of the breast, GIS, and GUS+gynecological organs compared to the cancers of the head and neck. ($p=0.000$) The Kruskal-Wallis analysis revealed statistically significantly higher age of patients with GIS malignancies compared to lung cancer ($p=0.012$). (Table 2)

Table 2. Examining of the relationship between diagnosis and variables

Tumour Site	**Head/neck** n(%)	**Lung** n(%)	**Breast** n(%)	**Gastrointestinal** n(%)	**GU + Gyn** n(%)	**Hematological** n(%)	**Chi-Square**	**p**
Gender								
Female	18(60)$_a$	10(32.3)$_a$	39(95.1)$_b$	16(40)$_a$	18(66.7)$_a$	9(45)$_a$	39.265	**0.000***
Male	12(40)$_a$	21(67.7)$_a$	2(4.9)$_b$	24(60)$_a$	9(33.3)$_a$	11(55)$_a$		
Metastasis								
No	5(16.7)	3(9.7)	5(12.2)	4(10)	3(11.1)	2(10)	1.030	0.960
Yes	25(83.3)	28(90.3)	36(87.8)	36(90)	24(88.9)	18(90)		
Chemotherapy							6.589	0.253
No	7(23.3)	4(12.9)	6(14.6)	10(25)	2(7.4)	6(30)		
Yes	23(76.7)	27(87.1)	35(85.4)	30(75)	25(92.6)	14(70)		
ECOG								
3	6(20)	5(16.1)	13(31.7)	13(32,5)	5(18.5)	3(15)	5,595	0,348
4	24(80)	26(83.9)	28(68.3)	27(67,5)	22(81.5)	17(85)		
Nutrition								
PEG	14(46.7)$_a$	8(25.8)$_{a,b}$	6(14.6)$_b$	4(10)$_b$	3(11.1)$_{a,b}$	6(30)$_{a,b}$	18.338	**0.000***
Oral	16(53.3)$_a$	23(74.2)$_{a,b}$	35(85.4)$_b$	36(90)$_b$	25(88.9)$_{a,b}$	14(70)$_{a,b}$		
Discharge Status								
Home	13(43.3)	13(41.9)	20(48.8)	12(30.0)	13(48.1)	6(30)	5,808	0,831
ICU	4(13.3)	5(16.1)	4(12.5)	5(12.5)	2(7.4)	3(15)		
Exitus	13(43.3)	13(41.9)	17(57.5)	23(57.5)	12(44.4)	11(55)		
	Mean±SD	**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**	**KW**	**p**
Age	66.27±18.07	**63.58±13.70**	66.59±14.08	**73.18±11.80**	71.07±11.15	73.85±12.86	14.721	**0,012* Dif.:4>2**
GCS	10.33±1.88	10.61±2.01	10.85±1.77	11.18±1.72	10.70±2.11	10.20±2.17	4.337	0.502
Haemoglobin(gr/dl)	100.00±20.88	99.06±22.81	102.22±17.67	102.35±22.57	102.81±20.70	103.95±22.07	1.746	0.883
MCV(fl)	86.08±9.33	89.62±6.17	84.90±19.41	89.49±6.52	87.58±6.97	86.04±5.64	5.223	0.389
Platelet($\times 10^3$ µl)	286.34±124.16	306.55±149.72	252.71±117.80	273.40±123.86	235.89±100.10	250.10±157.09	5.949	0.311
Ferritin(mg/l)	30.35±51.30	25.84±33.93	21.61±29.38	34.38±47.52	25.78±33.20	23.05±26.38	5.470	0.361
Iron(ug/dl)	45.43±29.09	47.03±36.36	43.76±24.51	48.63±36.72	47.81±29.03	50.85±32.38	0.699	0.983
Transferrin S.(%)	14.00±9.98	14.55±10.03	13.51±8.81	16.15±13.11	15.78±11.56	14.65±11.31	0.440	0.994
CRP(mg/l)	10.87±14.06	11.69±10.59	9.48±8.30	10.30±15.25	12.73±12.75	12.29±12.90	3.460	0.629
LOS (Days)	20.13±14.24	22.16±14.93	24.22±16.39	17.33±17.48	17.52±12.09	19.65±11.13	9.592	0.088

The correlation of anemia severity with ECOG scores and the use of a PEG was statistically significant across the groups ($p<0.05$). Since the cancers of the patients in our study were advanced, the ECOG performance scale scores were 3 or 4. ECOG scores of 4 ($p=0.045$) and the presence of a PEG ($p=0.036$) were statistically significantly more common among patients with severe anemia compared to those without (Fig.1)

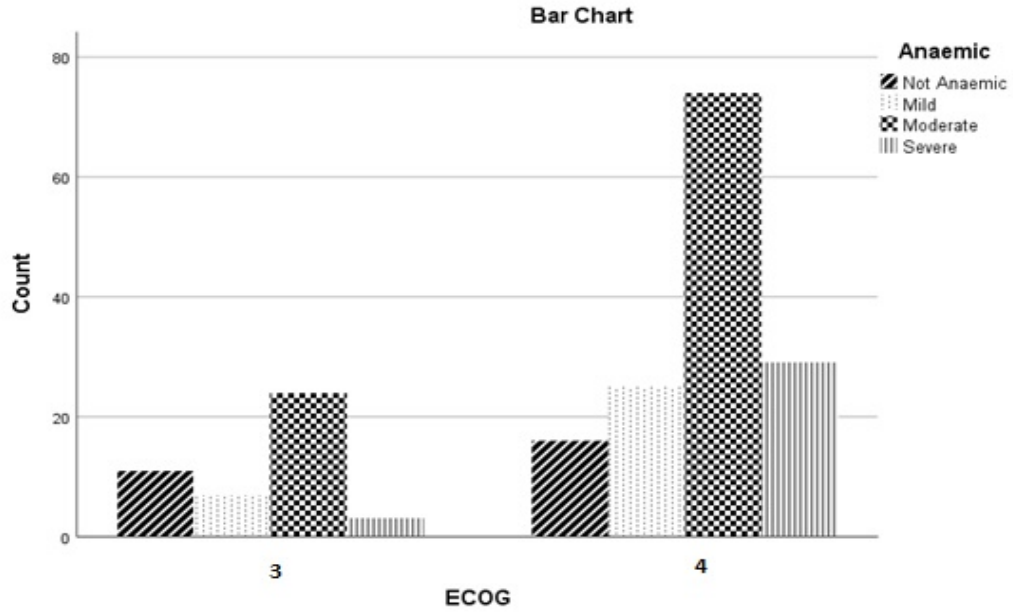

Figure 1. Relationship between ECOG and severity of anemia

Glasgow Coma Scales (GCS) were found to be significantly lower in patients with moderate anemia than those without anemia. (p=0.049). CRP levels were significantly higher in patients with severe anemia compared to patients without anemia and patients with mild and moderate anemia. (p=0.000) The type of cancer diagnosis was not statistically significantly correlated with the severity of anemia (p>0.05) (Table 3).

Table 3. Examining of the relationship between anaemia and variables

	Not Anemic n(%)	**Mild n(%)**	**Moderate n(%)**	**Severe n(%)**	**Chi-Square**	**p**
Gender						
Female	14(51.9)	21(65.6)	55(56.1)	20(62.5)	1.590	0.662
Male	13(48.1)	11(34.4)	43(43.9)	12(37.5)		
Diagnosis						
Head/neck	4(14.8)	4(12.5)	18(18.4)	4(12.5)		
Lung	5(18.5)	5(15.6)	11(11.2)	10(31.3)		
Breast	5(18.5)	10(31.3)	20(20.4)	6(18.8)	14.276	0.471
Gastrointestinal	6(22.2)	7(21.9)	20(20.4)	7(21.9)		
GU+Gyn	4(14.8)	4(12.5)	14(14.3)	5(15.6)		
Hematological	3(11.1)	2(6.3)	15(15.3)	0(0)		
Metastasis						
No	2(7.4)	3(9.4)	14(14.3)	3(9.4)	1.456	0.692
Yes	25(92.6)	29(90.6)	84(85.7)	29(90.6)		
Chemotherapy						
No	7(25.9)	8(25)	16(16.3)	4(12.5)	2.953	0.399
Yes	20(74.1)	24(75)	82(83.7)	28(87.5)		
ECOG						
3	$11(40.7)_a$	$7(21.9)_{a,b}$	$24(24.5)_{a,b}$	$3(9.4)_b$	8.033	**0.045***
4	$16(59.3)_a$	$25(78.1)_{a,b}$	$74(75.5)_{a,b}$	$29(90.6)_b$		
Nutrition					8.519	**0.036***

PEG	$1(3.7)_a$	$6(18.8)_{a,b}$	$23(23.5)_{a,b}$	$11(34.4)_b$		
Oral	$26(96.3)_a$	$26(81.3)_{a,b}$	$75(76.5)_{a,b}$	$21(65.6)_b$		
Discharge Status						
Home	12(44.4)	14(43.8)	41(41.8)	10(31.3)	4.485	0.611
ICU	1(3.7)	5(15.6)	11(11.2)	6(18.8)		
Exitus	14(51.9)	13(40.6)	46(46.9)	16(50)		
	Mean±SD	**Mean±SD**	**Mean±SD**	**Mean±SD**	**KW**	**p**
Age	71.78±13.77	70.09±14.55	67.94±13.61	67.91±15.69	2.264	0.519
GCS	11.48±1.93	11.09±1.59	10.44±1.98	10.50±1.81	7.862	**0.049* Dif:1>3**
CRP(mg/l)	6.45±5.33	7.48±7.66	11.33±12.57	17.35±16.47	16.895	**0.000* Dif: 4>1,2,3**
LOS (Days)	20.44±17.2	23.19±16.26	20.02±15.03	18.34±12.06	1.500	0.682

4. DISCUSSION

The study included patients with cancer who were treated in our PCU. Of the patients, 85.7% had anemia and 88.4% had metastases. All patients suffered from last-stage cancers. ECOG performance scale scores were 4 in 76.2% of the patients. Nonsurvivors in the PCU accounted for 47.1% of the study patients. Previous studies showed that anemia in cancer patients was a common problem with incidences of up to 90% (Knight et al., 2004, pp.11-26). Moreover, it was shown that anemia due to cancer could develop before antineoplastic therapy and it could unfavorably affect the therapeutic efficacy, prognosis, and quality of life (Madeddu et al., 2018, pp.1294). Despite the observations of the correlation between the several types of cancer and iron deficiency anemia in several studies, we could not detect such a significant correlation (Hashemi et al., 2017, pp. 192-198)

Inadequate nutrient intake and weight loss are major factors for early mortality in several types of cancer (Arends et al., 2017, pp. 11-48). Enteral feeding by several methods including a PEG has been shown to improve the quality of life, although mortality rates have not been reduced (Baldwin et al., 2012, pp. 371-385). In our study, 21.7% of all patients with advanced cancers in the PCU had a PEG, which was significantly more common in patients with head and neck cancers compared to those with the cancers of the breast and GIS. We considered that the frequency of patients with a PEG was low because patients had advanced cancers with low survival expectancy in our PCU. However, PEG is a common feeding method which is employed early to avoid dysphagia, dehydration, and consequent inadequate nutrient intake due to tumor location, chemotherapy, and radiotherapy in patients with head and neck malignancies (Mäkitie et al., 2022, pp. 1502-1523; Bojaxhiu et al., 2020, pp.281). Brito et al. (2020, pp. 3637), in their study with 472 patients, showed that anemia was more common in patients with PEG, and there was a positive correlation between hemoglobin levels and survival. The frequency of patients with a PEG was significantly higher among patients with severe anemia compared to those without in our present study. We have considered that the high frequency of having a PEG in severely anemic patients may be associated with severe problems interfering with the feeding and adequate nutrient intake in the early stages of cancer similar to the observations in patients with head and neck cancers (Arends et al., 2017, pp. 11-48).

The ECOG performance status has previously been shown to predict clinical outcomes including survival, response to chemotherapy, and the quality of life in cancer patients (Neeman et al., 2019, pp. 1460-1466). It has previously been shown that iron deficiency anemia is associated with significant impairment of immune, cognitive and physical functions and symptoms of fatigue, also in non-malignant diseases. (Verdon et al.,2003, pp 1124-26). For this reason, it is thought that iron deficiency anemia contributes to poor performance in cancer patients, as well as cancer itself and cancer treatments. In a previously conducted study, Ludwig et al. (2013, pp.1886–1892) showed that iron deficiency anemia was associated with poor performance in patients with advanced cancers and solid tumors. In our study on cancer patients receiving PC, too, we found poor performance in patients with severe anemia compared to patients without anemia. A prospective observational study showed that advanced cancer stages and the low performance status were associated with anemia due to cancer (Macciò et al., 2015, pp.124-132). GCS is a measure of change in the mental status of a patient, and it is a helpful instrument to predict mortality not only in acute brain injury but several types of disorders as well, with high values indicating a good prognosis (Lind et al., 2021, pp.399-404; Oh et al., 2019, pp. 520). In our study, GCS values were found to be significantly lower in patients with moderate anemia than those without anemia. We thought that poor performance and low GCS values indicate the relationship between anemia and poor prognosis in patients with cancer.

Park et al. (2015, pp. 42803-42812) found a positive correlation between anemia and the levels of CRP, ferritin, and hepcidin in cancer patients. Another study reported correlations of the prevalence and severity of anemia with the plasma levels of inflammatory markers including CRP, tumor necrosis factor, and fibrinogen in cancer patients (Natalucci et al., 2021, pp. 482). Consistently with those results, we found significantly higher CRP levels in patients with severe anemia compared to other groups in our present study. However, we could not find a correlation of the severity of anemia with the status at discharge and LOS.

5. CONCLUSION

We have shown that there may be an association between the severity of anemia and poor prognostic criteria including low GCS scores, poor performance and high CRP levels in PC patients with advanced cancers. We found a low incidence of PEG use in our cancer patients and observed that anemia was more severe in the patients with a PEG. This study shows that anemia is very common in cancer patients and the severity of anemia is associated with poor prognosis. Early assessment of anemia and the adequate intake of nutrients should be ensured in cancer patients during the disease course and its effects of such interventions on survival and prognosis should be investigated through large-scale studies.

6. REFERENCES

Arends, J., Bachmann, P., Baracos, V., Barthelemy, N., Bertz, H., Bozzetti, F., Fearon, K., Hütterer, E., Isenring, E., Kaasa, S., Krznaric, Z., Laird, B., Larsson, M., Laviano, A., Mühlebach, S., Muscaritoli, M., Oldervoll, L., Ravasco, P., Solheim, T., Strasser, F., Schueren, M., Preiser, JC. (2017). ESPEN guidelines on nutrition in cancer patients. Clin Nutr, 36, 11–48.

Baldwin, C., Spiro, A., Ahern, R., Emery, PW. (2012). Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. J Natl Cancer Inst, 104(5), 371-85.

Birgegard, G., Aapro, MS., Bokemeyer, C., Dicato, M., Drings, P., Hornedo, J., Krzakowski, M., Ludwig, H., Pecorelli, S., Schmoll, H., Schneider, M., Schrijvers, D., Shasha, D., Belle, SV. (2005). Cancer-related anemia: pathogenesis, prevalence and treatment. Oncology, 68, 3–11.

Bojaxhiu, B., Shrestha, BK., Luterbacher, P., Elicin, O., Shelan, M., Macpherson, AJS., Heimgartner, B., Giger, R., Aebersold, DM., Zaugg, K. (2020). Unplanned hospitalizations in patients with locoregionally advanced head and neck cancer treated with (chemo)radiotherapy with and without prophylactic percutaneous endoscopic gastrostomy, 15(1), 281.

Brito, M., Laranjo, A., Nunes, G., Oliveira, C., Santos, CA., Fonseca, J. (2020). Anemia and Hematopoietic Factor Deficiencies in Patients after Endoscopic Gastrostomy: A Nine-Year and 472-Patient Study**.** Nutrients, 12(12), 3637.

Clarke, H., Pallister, CJ. (2005). Impact of anemia on outcome in cancer. Clin Lab Haematol, 27, 1–13.

Demetri, GD., Kris, M., Wade, J., Degos, L., Cella, D. (1998). Quality-of-life benefit in chemotherapy patients treated with epoetin alpha is independent of disease response or tumor type: results from a prospective community oncology study. J Clin Oncol, 16, 3412– 25.

Dunn, A., Carter, J., Carter, H. (2003). Anemia at the end of life: prevalence, significance, and causes in patients receiving palliative care. J Pain Symptom Manag, 26(6), 1132–1139.

Hashemi, SM., Mashhadi, MA., Mohammadi, M., Ebrahimi, M., Allahyari, A. (2017). Absolute and Functional Iron Deficiency Anemia among Different Tumors in Cancer Patients in South Part of Iran, 2014. Int J Hematol Oncol Stem Cell Res, 11(3), 192–198.

Knight, K., Wade, S., Balducci, L. (2004). Prevalence and outcomes of anemia in cancer: a systematic review of the literature. Am J Med, 116, 11–26.

Lind. ML., Rosas, MM., McFarland, L., Taylor, L., Olson, S., Pergam, SA. (2021). Limits of the Glasgow Coma Scale When Assessing for Sepsis in Allogeneic Hematopoietic Cell Transplant Recipients. Nurs Res, 70(5), 399–404.

Ludwig, H., Müldür, E., Endler, G., Hübl, W. (2013). Prevalence of iron deficiency across different tumors and its association with poor performance status, disease status and anemia. Ann Oncol, 24(7), 1886–1892.

Macciò, A., Madeddu, C., Gramignano, G., Mulas, C., Tanca, L., Cherchi, MC., Floris, C., Omoto, I., Barracca, A., Ganz, T. (2015). The role of inflammation, iron, and nutritional status in cancer-related anemia: results of a large, prospective, observationalstudy. Haematologica, 100, 124–132.

Madeddu, C., Gramignano, G., Astara, G., Demontis, R., Sanna, E., Atzeni, V., Macciò, A. (2018). Pathogenesis and Treatment Options of Cancer Related Anemia: Perspective for a Targeted Mechanism-Based Approach. Front Physiol, 9, 1294.

Mäkitie, AA., Alabi, RO., Orell, H., Youssef, O., Almangush, A., Homma, A., Takes, RP., López, F., Bree, R., Rodrigo, JP., Ferlito, A. (2022). Managing Cachexia in Head and Neck Cancer: a Systematic Scoping Review. Adv Ther, 39(4), 1502-1523.

Natalucci, V., Virgili, E., Calcagnoli, F., Valli, G., Agostini, D., Zeppa, SD., Barbieri, E., Rita Emili, R. (2021). Cancer Related Anemia: An Integrated Multitarget Approach and Lifestyle Interventions. Nutrients, 13(2): 482.

Neeman, E., Gresham, G., Ovasapians, N., Hendifar, A., Tuli, R., Figlin, R., Shinde, A. (2019). Comparing Physician and Nurse Eastern Cooperative Oncology Group Performance Status (ECOG-PS) Ratings as Predictors of Clinical Outcomes in Patients with Cancer. Oncologist, 24(12), e1460–e1466.

Neoh, K., Page, A., Chin-Yee, N., Doree, C., Bennett, MI. (2022). Practice review: Evidence-based and effective management of anaemia in palliative care patients. Palliat Med, 36(5), 783–794.

Neoh, K., Stanworth, S., Pasricha, SR., Bennett, MI. (2016). Estimating prevalence of functional iron deficiency anaemia in advanced cancer. Support Care Cancer, 25(4), 1209–1214.

Oh, TK., Song, IA., Jeon, YT. (2019). Impact of Glasgow Coma Scale scores on unplanned intensive care unit readmissions among surgical patients.Ann Transl Med, 7(20), 520.

Oken, MM., Creech, RH., Tormey, DC., Horton, J., Davis, TE., McFadden, ET., Carbone, PP. (1982). Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol, 5(6), 649–655.

Park, S., Jung, CW., Kim, K., Kim, SJ., Kim, WS., Jang, JH. (2015). Iron deficient erythropoiesis might play key role in development of anemia in cancer patients. Oncotarget, 6(40), 42803–42812.

Teasdale, G., Jennett, B. (1974). Assessment of coma and impaired consciousness. A practical scale. Lancet (London, England), 2, 81-4.

Verdon, F., Burnand, B., Stubi, CL., Bonard, C., Graff, M., Michaud, A., Bischoff, T., Vevey, M., Studer, JP., Herzig, L., Chapuis, C., Tissot, J., Pécoud, A., Favrat, B. (2003). Iron

supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial. BMJ, 326, 1124–1126.

World Health Organisation (2011) Haemoglobin concentrations for the diagnosis and assessment of severity. [Online]. [Accessed 28 August 2013]. Available from: http://www.who.int/vmnis/indicators/haemoglobin.pdf