International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 03 Issue 07 July 2023

Page No: 1340-1346

DOI: https://doi.org/10.47191/ijmscrs/v3-i7-21, Impact Factor: 6.597

Effect of Baseline Hemoglobin Level on Prognosis in Nasopharyngeal Cancer Patients Receiving Chemoradiotherapy

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ABSTRACT

Objective: To explore retrospectively how pretreatment hemoglobin levels affected the prognosis of patients with nasopharyngeal cancer receiving chemoradiotherapy.

Methods: Clinical data of 97 nasopharyngeal cancer patients who received definitive chemoradiotherapy between 2000 and 2022 were analyzed. We accepted the cut-off value of hemoglobin as 11.0g/dL.

Results: In general, 13 (13%) of patients were Hb≤11g/dL, while 84 (86%) was Hb>11g/dL. Median survival times were 76 (95%CI 19-132) months and 205 (95%CI 157-252) months for Hb≤11g/dL and Hb>11g/dL patients, respectively. 1, 2, 3 and 5 year survival rates were 67.7%, 67.7%, 67.7% and 58% for Hb≤11g/dL and 90.3%, 83.6.2%, 75.2% and 66.1% for Hb>11g/dL patients, respectively, and this difference show no statistical significance (p=0.254). When we evaluated patients according to WHO criteria for anemia (hemoglobin <12g/dL (female) or <13g/dL (male)), the median survival time was 220 (95%CI 190-255) months for non-anemic patients whereas it was 76 (95%CI 0-157) months for anemic patients. 1, 2, 3 and 5 year survival rates were 92.5%, 87.6%, 78.8% and 68.9% for non-anemic and 75%, 67.5%, 63.7% and 55.8% for anemic patients, respectively. There was statistically significant difference between the two groups (p=0.013).

Conclusion: In our study, although Hb<11g/dl before chemoradiotherapy did not show a statistically significant difference in nasopharyngeal cancer patients, the median overall survival of 76 months in Hb≤11g/dL patients and 205 months for Hb>11g/dL patients. However, pretreatment anemia according to WHO criteria, and Hb≤11 g/dL in male patients were found to be independent adverse prognostic factors.

KEYWORDS: Nasopharyngeal carcinoma, Chemoradiotherapy, Hemoglobin, Prognosis

ARTICLE DETAILS

Published On:
18 July 2023

Available on:
https://ijmscr.org/

INTRODUCTION

Nasopharyngeal cancer (NPC) is a type of head and neck cancer, But when compared to other head and neck carcinomas, NPC has a different epidemiology, etiology, and clinical course. NPC incidence varies geographically, which points to a complex cause. Epstein-Barr virus (EBV) infection, environmental variables (such a high intake of preserved foods and smoking), and genetic predisposition all appear to combine in endemic communities to increase risk. Furthermore, it appears that exposure to a common agent early in life is a crucial element given the greater occurrence in younger individuals in high- and intermediate-risk areas. Alcohol use and tobacco use, which are traditional risk factors for other head and neck malignancies, are more frequently linked to nasopharyngeal carcinoma in the United States and Europe.

NPC has a distinct geographic distribution and is more common in the eastern and southern regions of Asia. Epidemiological trends over the past ten years have demonstrated that both its incidence and death have significantly decreased. These results most likely reflect alterations in lifestyle and environment, improved knowledge of the pathophysiology and risk factors, population screening, improvements in imaging tools, and personalized, all-encompassing chemoradiotherapy regimens.[1]

For NPC, definitive concurrent chemoradiotherapy (CRT) is the currently accepted standard of care, with T1N0M0 disease stage being the only one that can benefit from radiation (RT) alone.[2]

For many cancers, including the NPC, tumor hypoxia serves as a proxy indicator of treatment resistance. Elevated rates of

neo-angiogenesis and the synthesis of hypoxia-inducible factors culminate in the development of a novel aggressive tumor genotype that is highly resistant to free radical-mediated apoptosis.[3] A number of cancers treated with radiotherapy, notably cervical and head and neck cancers, have found hemoglobin (Hb) levels to be a predictive predictor. Evidence is increasing for NPCs as well.[4]

We accepted the Hb cut-off value of 11.0 g/dL in this retrospective investigation, despite the fact that the World Health Organization (WHO) criteria for anemia based on gender (Hb 12 g/dL (female) or 13 g/dL (male)) are fulfilled. We evaluated the effect of pre-treatment anemia on overall survival (OS) in patients with newly diagnosed NPC treated with curative CRT.

MATERIAL AND METHODS

Patient selection

This retrospective investigation has received permission from the institutional review board. (Project No. 2017-77, Kardeniz Technical University Faculty of Medicine Scientific Research Ethics Committee, Approval date: 08/05/2017). In order to identify NPC patients who received CRT between January 2000 and December 2022, it was retrospectively scanned, who were registered in the database maintained in the Radiation Oncology Clinic of Karadeniz Technical University Faculty of Medicine. Patients with metastatic disease and past or present malignancies were initially excluded from the study. Patients between the ages of 18 and 80 who had undergone biopsy-based pathological diagnosis, had undergone whole-body fludoxyglucose F 18 (18 F-FDG) positron emission tomography (PET)-CT imaging without evidence of metastasis, and had a Karnofsky Performance Score of at least 70 were included in the study. Renal function tests and liver function tests were performed before chemotherapy.

Treatment and Patients

Patients with T1N0M0 received RT only, but patients with T2 or N1, M0 received CRT. All patients had received 59.4 Gy and 54 Gy to the intermediate- and low-risk neck areas, as well as 70 Gray to the main tumor and all positive lymph nodes. The chemotherapeutic dosage was either 40 mg/m^2 once a week or three cycles 100 mg/m^2 of cisplatin (days 1, 21, and 42). While the 2BRT method was used from 2000 to 2010, the intensity modulated radiation therapy (IMRT) approach was intended to be used between 2010 and 2022.

Measures of the hemoglobin

According to the WHO guidelines, anemia is any pretreatment Hb 12 g/dL for females and Hb 13 g/dL for males. Pre-treatment anemia is the Hb value on the first day of RT. Post-treatment anemia is the 1st month control value after the first control after treatment.

Follow-up

For the first three years, follow-up appointments were planned every three months, and then every six months for the next three years. Fine-needle aspiration or biopsy was used to confirm distant metastases or locoregional insufficiency. A comprehensive physical examination, a repeat complete blood count, a biochemical test, a brain and neck MRI, a thorax and abdomen computed tomography, and any further procedures that were clinically necessary were performed at each appointment. Follow-up appointments continued from the time of the initial diagnosis until the final appointment or the date of death.

Statistical Analysis

The IBM SPSS Statistics 23 program was used to statistically evaluate the data. The key result was the correlation between pre-CRT Hb values and OS, or the interval between the commencement of CRT and death or the last follow-up. The Kaplan-Meier technique was used to calculate OS. To examine differences between subgroups and identify variables having independent prognostic significance on survival, a bilateral log-rank test was utilized. The established p value 0.05 statistical significance restriction applied to all significant tests and statistical significance.

RESULTS

Patient characteristics

In our database search, 154 NPC patients were enrolled, but 4 of them had not accepted CRT. Four patients younger than 18 years of age were excluded from the study. 6 patients had induction CT and the data of 43 patients was incomplete. As a result, 97 patients were eligible for analysis.

The patients ranged in age from 18-82 years, with a mean age of 49.64±14.51. Ninety-three patients were over the age of 19, compared to 4 individuals who were under 18.

The mean Hb value before RT was 13.07±1.74 g/dL (range:7.3-15.9) and after RT it was 11.77±1.55 g/dL (range:7.8-15.2g/dL).

Hb values of the patients were recorded before and after CRT. The Hb cut-off value was accepted as 11 and the patients were divided into two groups (≤11 g/dL and >11 g/dL).

Before RT, Hb was ≤11 g/dL in 13 patients (13%) and Hb was >11 g/dL in 84 (86%) patients. After RT, Hb was ≤11 g/dL in 34 patients (35%) and Hb was >11 g/dL in 63 (65%) patients.

34 patients (35%) were female, while 63 (65%) patients were male. Hb was ≤11 g/dL in 6 (6%) of male patients and Hb was >11 g/dL in 57 (59%). Hb was ≤11 g/dL in 10 (10%) female patients and Hb was >11 g/dL in 24 (25%).

In accordance with the stages, there were 4 (4%) patients in stage I, 18 (19%) in stage II, 54 (56%) in stage III, 21 (21%) in stage IVA.

HB was >11 g/dL in 4 (4%) patients with stage I. Hb was ≤11 g/dL in 3 (3%) of stage II patients and Hb was >11 g/dL in 15 (15%) patients. Hb was ≤11 g/dL in 8 (8%) of stage III patients and Hb was >11 g/dL in 46 (48%) patients. Hb was ≤11 g/dL in 4 (4%) of stage IVA patients and Hb was >11 g/dL in 17 (18%) patients.

Survival

The follow-up period was 79.4±72.1 (range:2-279) months. In all patients, median survival was 205 (95% CI 135-274) months, 1, 2, 3 and 5-year survival rates were 87.3%, 81.5%, 74.3%, and 65.1%.

Before CRT, median survival time was 76 (95%CI 19-132) months for Hb ≤11 g/dL patients whereas it was 205 (95%CI 157-252) for Hb >11 g/dL patients. 1, 2, 3 and 5 year survival rates were 67.7%, 67.7%, 67.7% and 58% for Hb ≤11 g/dL and 90.3%, 83.6%, 75.2% and 66.1% for Hb >11 g/dL patients, respectively. Between the two groups, there was no statistically significant difference (p=0.254), (figure 1.).

After CRT, the median survival times were 205 (95%CI 0-431) and 223 (95%CI 75-370) months for Hb ≤11 g/dL and Hb >11 g/dL patients, respectively. 1, 2, 3 and 5 year survival rates were 70.7%, 70.7%, 67% and 58.3% for Hb ≤11 g/dL and 93.3%, 85.9%, 78.3% and 67.9% for Hb >11 g/dL patients, respectively. Between the two groups, there was no statistically significant difference (p=0.243), (figure 2.).

In male patients, the median survival times were 11 (95%CI 4-17) and 223 (95%CI 117-328) months for Hb ≤11 g/dL and Hb >11 g/dL patients, respectively. 1, 2, 3 and 5 year survival rates were 41.7%, 41.7%, 41.7% and 41.7% for Hb ≤11 g/dL and 85.6%, 81.6%, 73.6% and 66.7% for Hb >11 g/dL patients, respectively. Between the two groups, there was a statistically significant difference (p=0.025), (figure 3.). In female patients, median survival time was 205 (95%CI 52-357) months for Hb >11 g/dL patients. 1, 2, 3 and 5 year survival rates were 85.7%, 85.7%, 85.7% and 68.6% for Hb ≤11 g/dL and 100%, 87.1%, 78.4% and 64.6% for Hb >11 g/dL patients, respectively. Between the two groups, there was no statistically significant difference (p=0.782), (figure 4.).

According to stage, in stage I patients, the median survival times were 10 months for Hb >11 g/dL patients. 1, 2, 3 and 5 year survival rates were 50%, 50%, 50% and 50% respectively. In stage II patients, the median survival time was 46 months for Hb ≤11 g/dL patients. 1, 2, 3 and 5 year survival rates were 100%, 100%, 100% and 50% for Hb ≤11 g/dL and 100%, 100%, 100% and 92.3% for Hb >11 g/dL patients, respectively. Between the two groups, there was no statistically significant difference (p=0.253). In stage III patients, the median survival time was 76 (95%CI 0-175) months for Hb ≤11 g/dL patients whereas it was 205 (95%CI 12-397) for Hb >11 g/dL patients. 1, 2, 3 and 5 year survival rates were 85.7%, 85.7%, 85.7% and 42.9% for Hb ≤11 g/dL and 90.9%, 83.2%, 72.7% and 61.5% for Hb >11 g/dL patients, respectively. Between the two groups, there was no statistically significant difference (p=0.808). In stage IVA patients, the median survival time was 8 (95%CI 4-11) months for Hb ≤11 g/dL patients whereas it was 161 (95%CI 0-366) for Hb >11 g/dL patients. 1, 2, 3 and 5 year survival rates were 33.3%, 33.3%, 33.3% and 33.3% for Hb ≤11 g/dL and 87.5%, 74%, 59.8% and 52.4% for Hb >11 g/dL patients, respectively. Between the two groups, there was no statistically significant difference (p=0.329). Our stage I patients had shorter survival times, which could be explained by the deaths of two of them: a 76-year-old man who passed away 5 months after treatment due to cardiac complications (coronary artery disease) and an 18-years boy who died 10 months after treatment from fungal sepsis.

The neutrophil and lymphocyte counts of the patients before to RT/CRT were used to determine neutrophil-to-lymphocyte ratio (NLR). The accepted NLR cut-off value was 3, and patients were split into two groups (3 and >3). According to NLR, in NLR ≤3 patients, the median survival time was 76 (95%CI 0-176) months for Hb ≤11 g/dL patients whereas it was 223 (95%CI 0-455) for Hb >11 g/dL patients. 1, 2, 3 and 5 year survival rates were 83.3%, 83.3%, 83.3% and 83.3% for Hb ≤11 g/dL and 93.8%, 86.7%, 81.7% and 70.3% for Hb >11 g/dL patients, respectively. Between the two groups, there was no statistically significant difference (p=0.768). In NLR >3 patients, the median survival time was 46 (95%CI 3-88) months for Hb ≤11 g/dL patients whereas it was 118 (95%CI 24-211) for Hb >11 g/dL patients. 1, 2, 3 and 5 year survival rates were 51.4%, 51.4%, 51.4% and 34.3% for Hb ≤11 g/dL and 85.9%, 79.7%, 67.3% and 60.7% for Hb >11 g/dL patients, respectively. Between the two groups, there was no statistically significant difference (p=0.183). Patient characteristics and survival are shown in Table 1.

When we evaluated patients according to WHO criteria for anemia (Hb <12 g/dL (female) or <13 g/dL (male)), the median survival times were 220 (95%CI 190-255) and 76 (95%CI 0-157) months for non-anemic and anemic patients, respectively. 1, 2, 3 and 5 year survival rates were 92.5%, 87.6%, 78.8% and 68.9% for non-anemic and 75%, 67.5%, 63.7% and 55.8% for anemic patients, respectively. Between the two groups, there was a statistically significant difference (p=0.013), (figure 5.).

In male patients, the median survival times were 223 (95%CI 0-462) and 62 (95%CI 0-146) months for non-anemic and anemic patients, respectively. 1, 2, 3 and 5 year survival rates were 89.2%, 84.5%, 77.1% and 68.5% for non-anemic and 59.1%, 59.1%, 51.7% and 43.1% for anemic patients, respectively. Between the two groups, there was a statistically significant difference (p=0.007), (figure 6.). In female patients, the median survival times were 205 (95%CI 0-433) and 118 (95%CI 0-275) months for non-anemic and anemic patients, respectively. 1, 2, 3 and 5 year survival rates were 100%, 94.4%, 82.6% and 69.9% for non-anemic and 92.3%, 76.9%, 76.9% and 59.8% for anemic patients, respectively. Between the two groups, there was no statistically significant difference (p=0.434), (figure 7.). Survival according to WHO criteria for anemic are shown in Table 2.

DISCUSSION

The current results of 97 NPC patients treated with CRT showed no statistically significant difference, although the median survival was 76 months in patients with Hb≤11 g/dL and 205 months in patients with Hb>11g/dL. However, when

we evaluated the patients according to the WHO criteria for anemia, there was a survival difference. Additionally, we demonstrated a stronger correlation between pretreatment Hb11.0 g/dL and considerably worse OS results in male patients.

Numerous research conducted over the past 25 years have revealed a link between Hb levels and local control of larynx, hypopharynx, oropharynx, bladder and cervix cancers. An unfavorable effect of radiotherapy is tumor hypoxia, which is particularly problematic for soft tissue sarcomas, uterine cervix cancer, and head and neck cancer.[5,6] Low Hb has been linked to undernutrition, weight loss, and cachexia due to cancer.[7]

Anemia is seen in more than 40% of head and neck cancer patients.[8] The Hb concentration determines the blood's ability to carry oxygen. So, hypothetically, we would anticipate that the majority of anemic individuals would have malignancies with low oxygen levels. Low Hb levels in peripheral blood have been shown to be a poor predictor of survival outcomes in these individuals[9,10] and are linked to a 75% greater risk of relative mortality.[11] Low Hb has also been proposed as a substitute biomarker for tumor hypoxia that is independent of smoking. Studies that have been cited as independent, poor prognostic variables for tumor hypoxia are available.[12] It has also been demonstrated that low Hb decreases the efficiency of radiation. The RTOG 85-27 head and neck research, in particular, was reanalyzed to validate the deleterious effects of anemia on loco-regional control and disease-free survival.[13]

It is still unclear exactly how Hb levels below 11.0 g/dL affect NPC patients' results. Animal research and mathematical models back up our Hb cut-off value of 11.0 g/dL. Tumoral oxygen delivery peaked at Hb levels around 11.0 g/dL and fell at lower Hb values, according to an investigation of the effect of anemia on tumor blood flow.[14]

In some studies, although Chua[15] et al. took the cut-off value of Hb 13.6 g/dL, in their predictive nomogram, Li[16] et al. found the Hb cut-off value to be 13.9 g/dL. In many recent studies, it was taken as 11 g/dL and was directly supported by the results.[4,17] The results of clinical studies in NPC further confirm the level of our Hb cut-off.

Mai et al., they stated that Hb <130 g/L before RT is a prognostic factor for local control of NPC and emphasized the importance of keeping Hb >130 g/L before and during treatment.[18] Zhang et al. accepted baseline Hb levels below 120 g/L in men and below 110 g/L in women as criteria for anemia. They also noted that pre-treatment anemia was an independent risk factor for poor prognosis.[19]

According to Topkan et al., anemia had a lower predictive value than pre-CRT Hb 11.0 g/dL in terms of progression-free survival and overall survival for NPC patients.[4] Although there was no disagreement in our investigation regarding the real impact of anemia on the outcomes determined using the suggested Hb11 g/dL cut-off value and the WHO anemia criteria, no statistically significant difference was detected in Hb11 g/dL individuals.

The key drawback of this study was that, because it was a retrospective examination of NPC patients from a single hospital, treatment heterogeneity was unavoidable. Even though our survival analysis took the post-treatment Hb level into account, only two time points for Hb levels were examined. Radiation therapy-related dynamic changes in Hb level were not investigated. Since most of the participants in our study came from the same area, our results cannot be compared to those from other areas. As a result, a sizable, multicenter, prospective study is needed to corroborate the results of the current investigation.

CONCLUSION

The median survival was numerically better in patients with Hb>11 g/dL in the entire study group, but no statistical difference was found. However, pretreatment anemia according to WHO criteria, and Hb≤11 g/dL in male patients were found to be independent adverse prognostic factors. Low Hb may be more common in patients with severe illness burden and poor performance status. To customize treatments based on such predictive indicators, additional research is necessary.

Acknowledgement: None

Authorship contribution statement

Consept and desing: BÇ, AB, MK

Acquisition of data: BÇ, AB, MK

Analysis and interpretation of data: BÇ, AB, MK

Drafting of the manuscript: BÇ, AB, MK

Critical revision of the manuscript for important intellectual content: BÇ, AB, MK

Statistical analysis: BÇ, AB, MK

Supervision: BÇ, AB, MK

Declaration of competing interest: None of the authors have potential conflicts of interest to be disclosed.

Ethical approval: Kardeniz Technical University Faculty of Medicine Scientific Research Ethics Committee, Project No. 2017-77 (08.05.2017)

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Funding: No financial support was received for this research.

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Table 1. Overall survival based on patient characteristics and Hb cut-off value <11.0 g/dL.

		Hb g/dL	n (%)	Median (95%CI)	p	1 y (%)	2 y (%)	3 y (%)	5 y (%)
General (Before RT)		≤11	13 (13%)	76 (19-132)	0.254	67.7	67.7	67.7	58
		>11	84 (86%)	205 (157-252)		90.3	83.6	75.2	66.1
General (After RT)		≤11	34 (35%)	205 (0-431)	0.243	70.7	70.7	67	58.3
		>11	63 (65%)	223 (75-370)		93.3	85.9	78.3	67.9
Sex	Male	≤11	6 (6%)	11 (4-17)	0.025	41.7	41.7	41.7	41.7
		>11	57 (59%)	223 (117-328)		85.6	81.6	73.6	66.7
	Female	≤11	10 (10%)	-	0.782	85.7	85.7	85.7	68.6
		>11	24 (25)	205 (52-357)		100	87.1	78.4	64.6
Stage	I	≤11	-	-	-	-	-	-	-
		>11	4 (4%)	10		50	50	50	50
	II	≤11	3 (3%)	46	0.253	100	100	100	50
		>11	15 (15%)	-		100	100	100	92.3
	III	≤11	8 (8%)	76 (0-175)	0.808	85.7	85.7	85.7	42.9
		>11	46 (48%)	205 (12-397)		90.9	83.2	72.7	61.5
	IVA	≤11	4 (4%)	8 (4-11)	0.329	33.3	33.3	33.3	33.3
		>11	17 (18%)	161 (0-366)		87.5	74	59.8	52.4

Table 2. Survival by WHO criteria for anemia

		Anemia (g/dL)	n (%)	Median (95%CI)	p	1 y (%)	2 y (%)	3 y (%)	5 y (%)
General		None	68 (70%)	220 (190-255)	0.013	92.5	87.6	78.8	68.9
		Yes	29 (30%)	76 (0-157)		75	67.5	63.7	55.8
Sex	Male	None (≥13g/dL)	16 (16%)	223 (0-462)	0.007	89.2	84.5	77.1	68.5
		Yes (<13g/dL)	47 (49%)	62 (0-146)		59.1	59.1	51.7	43.1
	Female	None (≥12g/dL)	13 (13%)	205 (0-433)	0.434	100	94.4	82.6	69.9
		Yes (<12g/dL)	21 (22%)	118 (0-275)		92.3	76.9	76.9	59.8
Stage	I	None	4	-		66.7	66.7	66.7	66.7
		Yes	-	-		-	-	-	-
	II	None	11	-	0.376	100	100	100	88.9
		Yes	7	-		100	100	83.3	66.7
	III	None	39	205 (128-281)	0.186	94.6	88.5	75.7	65.2
		Yes	15	76 (9-142)		77.9	70.1	70.1	61.4
	IVA	None	13	223	0.091	83.3	75	66.7	57.1
		Yes	8	16 (0-52)		60	45	30	30

Figures:

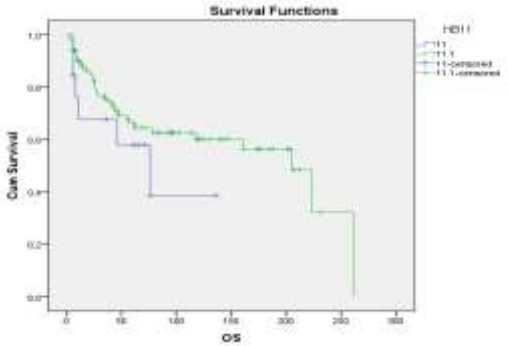

Figure 1. Survival by Hb cut-off value <11 g/dL level in patients before CRT

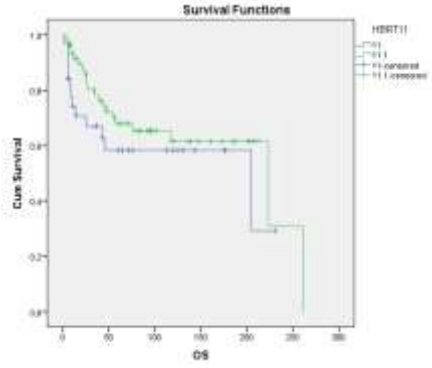

Figure 2. Survival by Hb cut-off value <11 g/dL level in patients after CRT

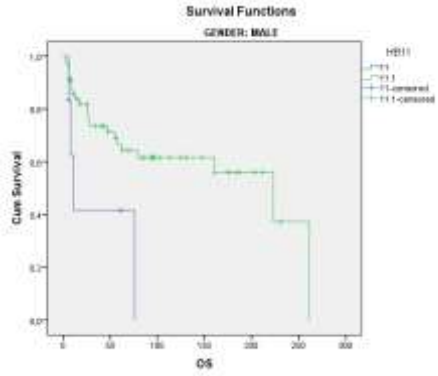

Figure 3. Survival in male patients by Hb cut-off value <11 g/dL level

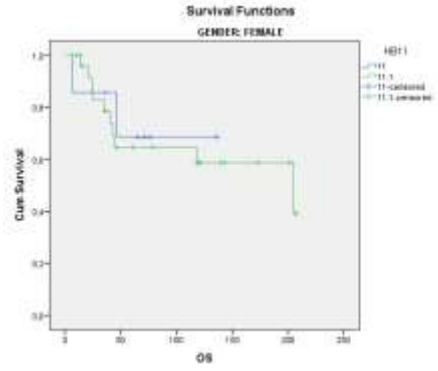

Figure 4. Survival in female patients by Hb cut-off value <11 g/dL level

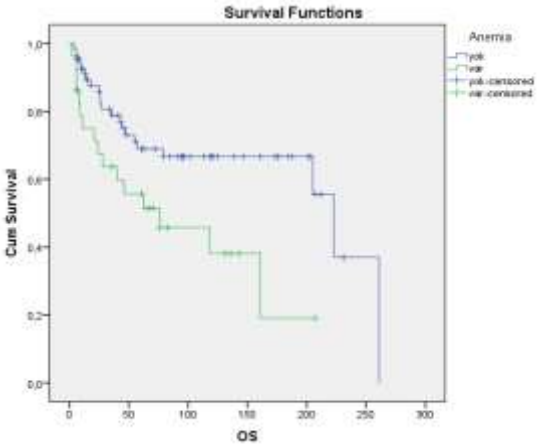

Figure 5. Survival by WHO criteria for anemia

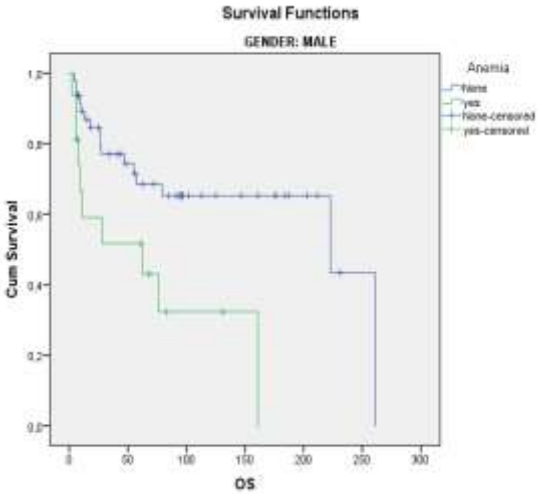

Figure 6. Survival by WHO criteria for anemia in male

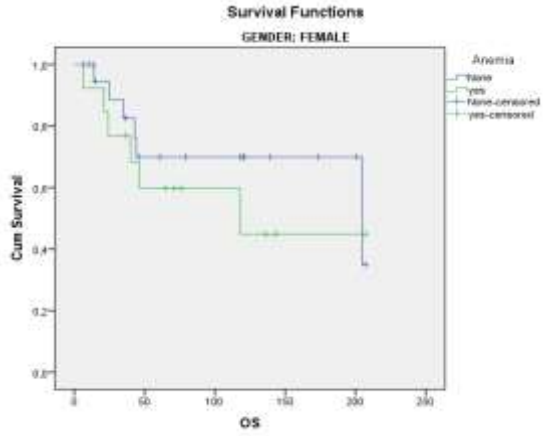

Figure 7. Survival by WHO criteria for anemia in female