Pre-treatment Complete Blood Count as a Predictor of Overall Survival in Pediatric Patients of age ≤18 Years Presenting with Osteosarcoma

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ABSTRACT

Introduction: Osteosarcoma is the most common malignancy of bone. Multi-disciplinary treatment has improved clinical outcomes up to 70%. Factors such as alkaline phosphatase, lactate dehydrogenase, and post-chemotherapy tumor necrosis factor-alpha play a key role in predicting prognosis. However recently, due to cost-effectiveness of inflammatory markers derived from complete blood count have gained popularity in determining survival rates.

Methods: The retrospective study was conducted in pediatric population who were below the age of 18 years. 73 patients meeting the inclusion criteria were included in the study who were enrolled from 2005 to 2015. Medical records were reviewed and their survival was analyzed based on the hematological indices using complete blood count and other medical and surgical variables.

Results: Out of these 73 patients, 54.8% were male and their percentage survival was found to be 38.4%. The most common site of the presentation was tibia (47.9%). In univariate analysis, pre treatment hemoglobin levels or hemoglobin before treatment, completion of neoadjuvant therapy and adjuvant therapy, pathological fracture on presentation, metastasis, surgery performed, TLC ≥0.6875, NC ≥0.471, and LC ≥0.2343 were found to be significant risk factors of death. In multivariate analysis metastasis during or after treatment, hemoglobin levels <11mg/dl and TLC ≥0.6875 were the found to be the major factors of death.

Conclusion: None of the pre-treatment indices taken from CBC proved to predict survival except hemoglobin (<11 mg/dl) and TLC (≥0.6875) which were associated with an increased risk of disease progression along with metastasis either during or after treatment

Keyword: Complete blood count, survival, osteosarcoma

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INTRODUCTION

Osteosarcoma is one the most common primary bone malignancy reported in adolescents and young adults.[1] It accounts for 3% to 5% of all the juvenile cancers and no more than 1% of all the malignant tumors in adults.[2,3] Nonetheless, it is rare and constitutes 5% of all the childhood cancers.[4] A US-based study reported the global incidence to be 3 to 4.5 cases per 1 million children, adolescents, and young adults (0-24 years of age) per year.[5]

The incidence of osteosarcoma in Asia reported previously from 1993 to 1997 was 2.5% vs 4.1% in male vs female of age 0-24 years, 1.1% vs 1.5% in male vs female of age 25-59 years and 2.4% vs 3.1% in male vs female of age ≥60 years.[3] Since, Asia constitutes 60% of the entire world population and a large portion (50%) of the worldwide malignancies, it had been estimated that the

incidence of cancer cases in Asia will increase from 6.1 million in 2008 to 10.6 million in 2030.[6]

Development of osteosarcoma is linked with genetic mutations in certain proto-oncogenes such as retinoblastoma gene, p53 and over expression of MDM2[7]. Moreover, additional studies have shown that Inflammation plays an essential role in progression of tumor as it accelerates angiogenesis and metastasis. It disrupts the adaptive immune system thus affecting hormonal and chemotherapy responses[8,9]. Using this inflammatory concept a number of anti-inflammatory drugs are being used in chemotherapy for improving survival[10].

Medical procedure was the main-stay treatment in previous three decades which had a 5-year survival rate was 10%[1,11]. Furthermore, poor prognosis has also been observed in patients presenting with metastatic osteosarcoma and a 5-year survival rate of 20% to 30% due to surgical removal of metastasis and chemotherapy[12]. However, multidisciplinary approach towards has proved beneficial towards patient care. By combining both medicine and surgery, the expected 5-year survival rate has increased up-to 70%.[8]

Alkaline phosphatase, lactate dehydrogenase and post-chemotherapy tumour necrosis are some of the well known prognostic factors for osteosarcoma[13], but due to the role of inflammation in tumor growth, inflammatory markers have gained popularity in trying to predict the outcome and survival rate of patients with tumor. Inflammatory markers and hematological indices derived from complete blood count are not only easily and readily available but are also cost-effective.

There is increasing imminent data using these indices in predicting the survival of osteosarcoma patients. However, there is an absence or lack of data from our part of the world. We therefore, present our experience of assessing the survival at five years using hematological indices and compare our results with international data.

METHODOLOGY

A retrospective analysis was conducted of all consecutive patients aged below 18 years diagnosed with osteosarcoma during the period of 2005 to 2015. Ethical board approval was obtained from Interactive Research and Development. Patients with metastasis on presentation and those with an incomplete medical record were excluded from the study. Patient having clinical evidence of infection or any other inflammatory conditions at presentation and those who were treated with anti-cancer therapy or non-steroid anti-inflammatory drug (NSAID) previously were also excluded.

Medical records of all eligible patients were analyzed. Their age, gender, previous medical and surgical history, neo-adjuvant and/or adjuvant therapy given, pre-diagnosis complete blood count, tumor location, histologic type, pathological fracture, local recurrence and the occurrence of metastasis during or after completion of treatment were recorded. Patient's follow up was reviewed and their survival was assessed from the time of registration to the hospital till October 2020. Those patients whose survival or mortality was not known were contacted through phone on the same day and date (10th Oct 2020) and data was collected from them. The pre-diagnosis complete blood count was reviewed.

Statistical analysis: The collected data were entered and analyzed using SPSS version 24.0. Mean± SD and median (IQR) were computed for all the quantitative variables such as age, neutrophil count, lymphocyte count, monocyte count and platelets, neutrophil to lymphocyte ratio, and platelet to lymphocyte ratio. Frequency and percentage were computed for all the categorical variables such as gender, survival status, neo-adjuvant, and adjuvant therapy. Pearson Chi-Square test/Fisher's Exact test was applied as appropriate to assess association between various categorical variables and survival status. Independent sample T-test/Mann Whitney U test and Median test- were applied as appropriate to assess significant differences in quantitative variables between alive and expired patients. Youden's index was used to calculate the cut-off values of neutrophil count, lymphocyte count, monocyte count and platelets, neutrophil to lymphocyte ratio, and platelet to lymphocyte ratio. Univariate and multivariable cox-regression analyses were performed to assess the risk factors associated with death. The proportional hazard assumptions were checked using Schoenfeld residuals test and by assessing the significance of slope of time*independent variables interaction. All significance tests were two-tailed and the results were considered statistically significant when the p-value < 0.05.

RESULTS

A total of 135 patients were enrolled during the time-period 2005 to 2015. Survival status of the patients was confirmed by calling them in the present year on the same date. The analysis was performed on 73 patients who had a complete medical and surgical record and their survival status were known (Fig 1).

Out of these 73 patients, 40 (54.8%) were male and 28 (38.4%) patients survived (Fig1). Median (IQR) age and duration of survival were 14 years (IQR: 11-15 years) and 15 months (IQR: 5-66 months) respectively. Nearly half of the patients had tumor on tibia (n=35, 47.9%), followed by femur (n=20, 27.4%), and humerus (n=9, 12.3%, Fig 2). Amputation was done in 29 (39.7%) patients (Fig 1). 16 (21.9%) patients had pathological fractures, and 20 (27.4%) patients had metastasis during or after completion of treatment (Fig 1).

The study data reported no significant median difference in the hemoglobin, total leucocytes and neutrophil count between the alive and expired patients (p=0.122, 0.313 and 0.379 respectively, Table 1) but there was a statistically significant difference in the distribution across the survival status. Results revealed that patients who survived had significantly higher hemoglobin levels in comparison to the lapsed patients (Mean rank: 43.65 vs 33.10 p=0.040, Table 1). Similarly, patients who survived were found to have lower total leucocytes, and neutrophil count at the time of presentation in comparison to those who expired (Mean rank: 28.67 vs 41.89, p=0.010; 29381 vs 41.22, p=0.027 respectively, Table 1).

Furthermore, no significant association of gender and recurrence of the disease was found with the survival status (p=0.630 and 0.299 respectively, Table 2). Moreover, the data showed 100% mortality rate in patients who did not undergo surgery, and who did not have neoadjuvant therapy, while those who underwent surgery and had neoadjuvant therapy had 51.9% and 41.5% survival rate respectively (p=0.000 and 0.023 respectively, Table 2). Also, it was found that the survival rate was significantly higher in patients who received adjuvant therapy in comparison to those who did not have adjuvant therapy (58.1% vs 6.9%, p=0.000, Table 2) Univariate and multivariable cox-regression analyses were also performed to assess the risk factors associated with death. In univariate analysis, hemoglobin, hematocrit, given neoadjuvant therapy and adjuvant therapy, pathological fracture on presentation, metastasis, and surgery performed were found to be significant risk factors of death. Univariate analysis showed that there patients who had HB <11 at the time of admission, who were not given complete neoadjuvant and adjuvant therapy, who presented with fracture, who developed metastasis during or after treatment and who did not undergo surgery had 1.83, 2.46, 3.77, 2.44, 11.66, and 3.7 times higher risk of progression in comparison to other patients (p=0.042, 0.018, 0.000, 0.006, 0.000 and 0.000 respectively, Table 3). Also, results showed that patients presenting with TLC ≥0.6875, NC ≥0.471and LC ≥0.2343 had 3.8, 2.0 and 1.9 times higher risk of progression as compared to others (p=0.011, 0.041, and 0.042 respective, Table 3) Moreover, females, patients with pre-treatment platelet/lymphocyte ratio≥96.86 and lymphocyte/monocyte ratio ≥16.58 were found to have 1.14, 1.2 and 1.73 times higher risk of progression respectively though the results were not statistically significant (p=0.649, 0.611 and 0.186 respectively, Table 3).

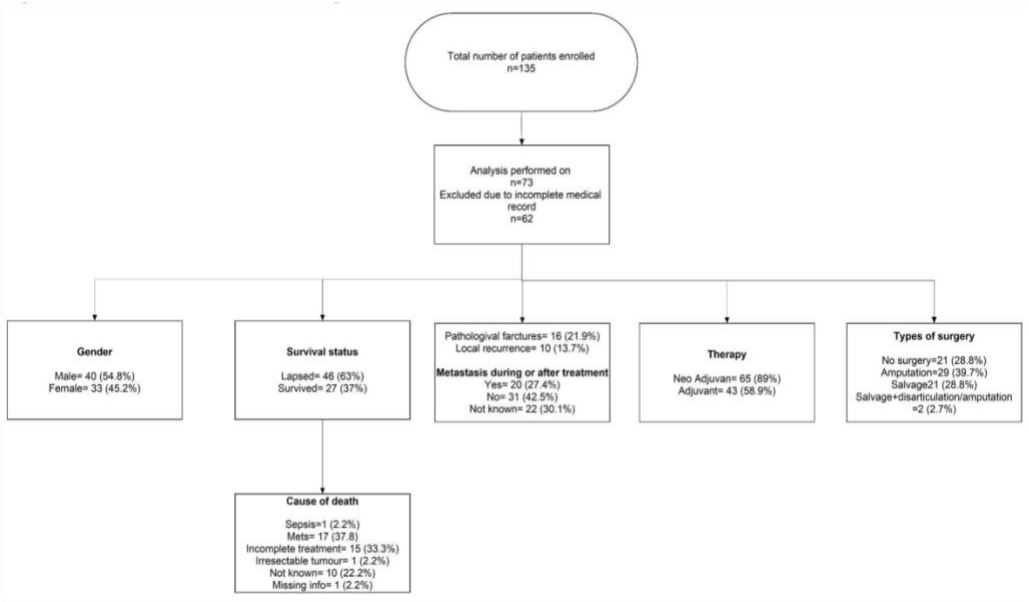

Figure 1: Flowchart of the study

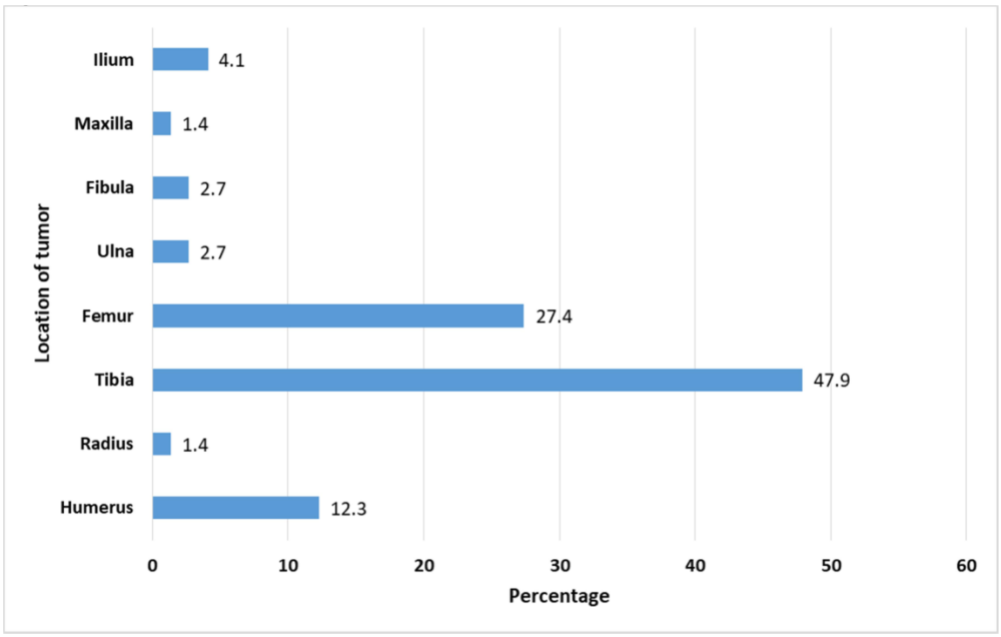

Fig 2: Location of tumor

Table 1: Difference in total CBC count between alive and expired patients

	Died			Alive			Overall			P-value
	Mean ± SD	Min-Max	Median (IQR)	Mean ± SD	Min-Max	Median (IQR)	Mean ± SD	Min-Max	Median (IQR)	
Hemoglobin	10.4 ± 2.5	3.6 - 14.1	10.9(9.2 - 12.3)	11.6 ± 2	4.9 - 14.7	12(10.4 - 12.8)	10.9 ± 2.4	3.6 - 14.7	11.1(9.8 - 12.6)	0.122 ŧ 0.040*
Hematocrit	32.2 ± 7.7	13 - 41.9	35.2(28.8 - 37.3)	35.1 ± 6	18 - 44.9	36(32.2 - 38.2)	33.2 ± 7.2	13 - 44.9	35.7(31.3 - 37.7)	0.451 ŧ 0.185
Mean corporsule volume	77 ± 11.9	19.5 - 100	76.8(73 - 83.3)	79.6 ± 6.5	65 - 88	80(77 - 86)	77.9 ± 10.3	19.5 - 100	79.5(73.9 - 83.6)	0.566 0.301
Total leucocyte count per 10,000	1.10 ± 0.68	0.30 – 4.92	0.94 (0.78-1.21)	0.81 ± 0.23	0.42-1.44	0.82 (0.62-0.96)	0.1 ± 0.58	0.30-4.92	0.88 (0.74-1.07)	0.313ŧ 0.010*ł
Neutrophil %	65 ± 10.9	44 - 85	64(57.5 - 75.5)	61.8 ± 11	44 - 80	63(52 - 67)	63.8 ± 11	44 - 85	64(55 - 71.5)	0.239ŧ
Neutrophil platelet score	0.6 ± 0.7	0 – 2	0(0 - 1)	0.3 ± 0.6	0 - 2	0(0 - 1)	0.5 ± 0.7	0 - 2	0(0 - 1)	0.455ŧ 0.224ł
Neutrophil count per 10,000	0.75 ± 0.59	0.14-4.03	0.58 (0.46-0.83)	0.504 ± 0.18	0.19-0.82	0.47 (0.39-0.64)	0.66 ± 0.49	0.14-0.42	0.54 (0.42-0.76)	0.379 ŧ 0.027*
Lymphocytes %	28.3 ± 11	10 - 50	28.5(19.5 - 35)	29 ± 9.3	13 - 46	30(23 - 36)	28.6 ± 10.3	10 - 50	29(21 - 35.5)	0.765ŧ
Lymphocytes count per 10,000	0.28 ± 0.11	0.12-0.57	0.26 (0.22-0.31)	0.23 ± 0.09	0.09-0.52	0.23 (0.16-0.27)	0.26 ± 0.10	0.09-0.57	0.24 (0.19-0.30)	0.172ŧ 0.050ł
Monocytes %	3.4 ± 1.8	0 – 8	3(2 - 5)	3.8 ± 2.1	1 - 9	4(2 - 5)	3.6 ± 1.9	0 - 9	3(2 - 5)	0.653ŧ 0.642ł
Monocytes count	379 ± 358.1	0 - 2460	313(209.8 - 450)	316.5 ± 217.5	84 - 1008	264(164 - 412)	355.9 ± 313.3	0 - 2460	300(176.5 - 443.5)	0.379ŧ 0.285ł
Platelets count per 10,000	35.8 ± 14.1	19.1-73.6	31.4 (25.9-42.07)	32.68 ± 8.92	14.9-50.1	32.8 (25.4-41.0)	34.7± 12.5	14.9-73.6	32.3 (25.8-41.1)	0.566ŧ 0.736ł
Neutrophil lymphocyte ratio	2.9 ± 1.9	0.9 - 8.5	2.2(1.7 - 3.8)	2.5 ± 1.4	1 - 6.2	2.1(1.5 - 2.9)	2.8 ± 1.7	0.9 - 8.5	2.2(1.5 - 3.4)	0.693ŧ 0.511ł
Platelet lymphocyte ratio	145.7 ± 72.1	54.8 - 355	121.9(97 - 194.7)	169.9 ± 100	48 - 474.2	145.2(96.8 - 178.3)	154.6 ± 83.7	48 - 474.2	129(97 - 184.6)	0.289ŧ 0.411ł
Lymphocyte monocyte ratio	9.4 ± 6.4	0 – 28	8.7(4.6 - 12.1)	9.9 ± 6.2	3 - 29	9(5.1 - 13)	9.6 ± 6.3	0 - 29	9(4.9 - 12.3)	0.829 ŧ 0.689

*P-value<0.05, ŧ Median test, ł Mann-Whitney U test

In multivariable analysis, all the variables with p-value<0.25 and of biological significance were included. Final model showed that patients who developed metastasis during or after treatment had 10.22 times higher risk of death adjusting for pre-treatment HB and TLC (p=0.000, Table 3). Furthermore, it was found that patients with pre-treatment HB <11 had a 2.3 times higher risk of progression adjusting for metastasis and pre-treatment TLC (p=0.059, Table 3). Similarly, patients who had pre-treatment TLC≥0.6875 had 3.1 times higher risk of death adjusting for metastasis and pre-treatment HB, although the result was not statistically significant (p=0.145, Table 3).

Table 2: Association of study participants' characteristics with survival status

	Final Outcome			P-value
	Died	**Survived**	**Total**	
Gender				
Male	24(52.2)	16(59.3)	40(54.8)	0.630ǂ
Female	22(47.8)	11(40.7)	33(45.2)	
Total	46(100)	27(100)	73(100)	
Surgery				
Yes	25(48.1)	27(51.9)	52(100)	0.000*ǂ
No	21(100)	0(0)	21(100)	
Total	46(63.0)	27(37.0)	73(100)	
Neoadjuvant				
Yes	38(58.5)	27(41.5)	65(100)	0.023*ǂ
No	8(100)	0(0)	8(100)	
Total	46(63)	27(37)	73(100)	
Adjuvant				
Yes	18(41.9)	25(58.1)	43(100)	0.000*ǂ
No	27(93.1)	2(6.9)	29(100)	
Total	45(62.5)	27(37.5)	72(100)	
Mets				
Yes	20(80)	0(0)	20(39.2)	0.000*ǂ
No	5(20)	26(100)	31(60.8)	
Total	25(100)	26(100)	51(100)	
Fracture				
Yes	15(32.6)	1(3.7)	16(21.9)	0.004*ǂ
No	31(67.4)	26(96.3)	57(78.1)	
Total	46(100)	27(100)	73(100)	
Recurrence				
Yes	7(24.1)	3(11.1)	10(17.9)	0.299ǂ
No	22(75.9)	24(88.9)	46(82.1)	
Total	29(100)	27(100)	56(100)	
*P-value<0.05, **P-value<0.0001, ǂ Pearson Chi Square test,ǂ Fisher's Exact test				

Table 3. Univariate and multi-variant analysis of factors associated with survival

	Univariate analysis			Multivariable analysis		
	HR	**95% CI**	**P- value**	**HR**	**95% CI**	**P-value**
Gender						
Female	1.140	0.641-2.042	0.649	-	-	-
Male	**Ref**					
Hematocrit	0.958	0.923-0.995	0.028*			
Total leucocytes count per 10000	1.32	0.96-1.82	0.086	-	-	-
Neutrophils count per 10000	1.38	0.95-2.00	0.093	-	-	-
Lymphocytes count per 10000	12.20	0.81-184.5	0.071	-	-	-
Platelet count per 10000	1.02	0.996-1.042	0.107			

Neutorphil count per 10000	1.38	0.95-2.004	0.093			
neutrophil lymphocyte ratio	1.08	0.923-1.27	0.327			
platelet lymphocyte ratio	0.999	0.995-1.002	0.484			
lymphocyte monocyte ratio	0.992	0.943-1.042	0.739			
Hemoglobin						
<11	1.83	1.02-3.26	0.042*	2.27	0.97-5.3	0.059
≥11	**Ref**					
Neoadjuvant						
No	2.46	1.13-5.32	0.018*	-	-	-
Yes	**Ref**					
Adjuvant						
No	3.77	2.03-7.0	0.000**	-	-	-
Yes	**Ref**					
Fracture						
Yes	2.44	1.3-4.59	0.006*	-	-	-
No	**Ref**					
Metastasis						
Yes	11.66	4.23-32.13	0.000**	10.22	3.57-29.24	0.000**
No	**Ref**					
Surgery						
No	3.70	2.01-6.81	0.000**	-	-	-
Yes	**Ref**					
Total leucocytes count per 10000						
<0.6875	**Ref**					
≥0.6875	3.81	1.36-10.7	0.011*	3.06	0.68-13.8	0.145
Neutorphil count per 10000						
<0.47	**Ref**					
≥0.4705	2.033	1.031-4.011	0.041*			
Lymphocytes count per 10000						
<0.2343	**Ref**					
≥0.2343	1.93	1.025-3.63	0.042*			
platelet lymphocyte ratio						
<96.86	**Ref**					
≥96.86	1.200	0.595-2.42	0.611			
lymphocyte monocyte ratio						
<16.58	**Ref**					
≥16.58	1.728	0.768-3.89	0.186			
*P-value<0.05, **P-value<0.0001, Cox regression analysis; HR: Hazard ratio						

DISCUSSION

Pre-treatment complete blood count (CBC) was extensively studied in this study and its role in predicting the survival rate of pediatric patients presenting with osteosarcoma was assessed. Our study showed 37% ≥3-year survival rate and 32.9% ≥3-year relapse-free survival rate in Pakistani pediatric population Hospital from 2005 to 2015. The survival rates in our pediatric population were significantly lower than the survival rate reported in the literature. Morsay AM et al[14] estimated 3-year and 5-year overall survival rate of 50.9% and 42.1% respectively. Haddox CL et al[15] reported a 3-year event-free survival rate of 60% and 58% in pediatric (<18 years) and young adults (18-40 years) cohort. Haglitner MM et al[16] reported 5-year overall survival rate of 66.9% ± 0.15, the 10- year overall survival rate of 64.6% ± 0.23; and the 20-year Overall survival rate of 62.3% ± 0.82. Lee JA et al[17] reported 5-year event-free survival rate of 64.5±9.3% and 58.2±9.1% in preadolescents and adolescent group.

Significant association between inflammatory markers and prognosis of osteosarcoma has been previously reported in studies from western world[18-21]. High pretreatment neutrophils count and low level of lymphocyte/monocyte ratio are reported to be poor prognostic factors[22]. A meta-analysis showed pre-treatment neutrophil/lymphocyte ratio (NLR) to be a significant marker associated with survival[19].

Study reported that higher pre-operative NLR is associated with reduced 5-year overall survival (HR 3.75, 95% CI 1.24 to 11.37) and 3 year disease/relapse free survival (HR 2.43, 95% CI 0.84 to 7.05)[19]. Our study results are comparable to that of literature. Our study also showed higher pre-treatment total leucocyte, neutrophil and lymphocyte counts in deceased patients as compared to the patients who survived, but the results were not statistically significant. Moreover, the results of our study are comparable to Li et al[23] reporting slightly shorter but statistically insignificant disease-free survival in patients with pre-treatment platelets ≥300×109/L (HR: 1.13 (95% CI: 0.64±2.00), p=0.666) .

Our study was primarily based on the pediatric population and most of the literature showed prominent correlation between survival and inflammatory markers which considerable adult population had. Similarly, these inflammatory markers were also found to be a prognostic factor in renal clear cell cancer[24], breast[25] and gastric cancer[26-28] which are tumors of old age grouped people. Thus comparable data of similar age group was not present to the best of our knowledge.

Moreover, higher hemoglobin levels were linked with better survival which was also reported by Prison et al[19]. There were other factors too which were related to survival and were also dominant in our study. They were also previously documented, such as completed neoadjuvant and adjuvant therapy, pathological fracture on presentation, metastasis, and surgery performed.

Our results did not show similar significance as reported earlier. These could be based on the different age groups that were included. However, it is worth noting that this study is the first attempt to evaluate the prognostic significance of these inflammation-based prognostic indices in pediatric patients with osteosarcoma in a developing country. The retrospective study can also be a potential limiting factor in determining a significant association. We therefore recommend a larger scale prospective study since these inflammatory indices are derived from simple, cost-effective and routinely done complete blood count. If a significant association is established, this could be of great value for the patients in developing countries.

CONCLUSION

Metastasis taking place during or after completion of therapy was a significant risk factor for determining the mortality of the patients. In addition, using complete blood count, lower pre-treatment hemoglobin level (level < 11mg/dl) and TLC ≥0.6875 were found to be associated with increased risk of disease progression.

Conflict of Interest: None

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