The Role of The Ratio of Neutrophil Lymphocyte Platelet Lymphocyte and Lymphocyte Monocyte as A Prognostic Factor for Patients with Muscle Invasive Bladder Cancer at Prof Dr. I.G.N.G. Ngoerah Hospital Denpasar

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ABSTRACT

Background: Bladder cancer is the type of malignancy most frequently reported in the field of urology, where muscle-invasive bladder cancer (MIBC) accounts for around 25-30% of all cases with this malignancy. Bladder cancer morbidity and mortality are reported to be most common in Asia, where developing countries have a higher mortality-to-morbidity ratio. Several studies have shown the utility of simple laboratory inflammatory marker tests such as NLR, PLR, and LMR as predictors of outcomes in cases of other malignancies. ***Objective:*** To prove the value of NLR, PLR, and LMR can show the overall survival rate in post-cystectomy muscle-invasive bladder cancer patients. ***Method:*** This type of study is a retrospective cohort study to prove the value of NLR, PLR, and LMR as independent predictors in predicting outcomes in patients with MIBC. The sample was selected using consecutive sampling by selecting subjects who met the research criteria in the period January 2015 to December 2021 involving 50 MIBC patients who have undergone curative procedures at Prof. I. G. N. G Ngoerah Hospital Denpasar. ***Results:*** The chi-square test showed that there was a significant association between NLR and MIBC mortality (OR=24.8; 95%CI=2.75-223.2; p=0.001) and between PLR and MIBC mortality (OR=10.8; 95%CI=1.93-60.9; p=0.004). There was no relationship between LMR and MIBC mortality (p=0.561). Meanwhile, the results of multivariate analysis using the Cox regression test showed that high NLR was an independent predictor of MIBC mortality after controlling for confounding variables (OR=27.728; 95%CI=1.443-532.756; p=0.028). ***Conclusion:*** High NLR and PLR can indicate a poor overall survival rate in MIBC patients, but only NLR was proven to be significant as an independent predictor for the outcome of MIBC patients.

Keywords: bladder cancer; LMR; MIBC; NLR; PLR; Predictors.

INTRODUCTION

Bladder cancer is the most commonly reported malignancy in urology (Al-Husseini et al., 2019; WHO, 2019a), with muscle-invasive bladder cancer (MIBC) accounting for approximately 25-30% of all cases with this malignancy (Zhang et al., 2020). Bladder cancer morbidity and mortality are reported to be most common in Asia, where developing countries have a higher mortality-to-morbidity ratio (WHO, 2019a). The outcomes of patients with these cancers are reported to be poor (Kaiser et al., 2018), so the role of biomolecular prognostic markers that are easy to perform yet have precise diagnostic value are urgently needed for more specific and individualized management (Kaiser et al., 2018; Wu et al., 2020; Zhang et al., 2020).

GLOBOCAN data in 2020 reported that there were approximately 549,393 new cases of bladder cancer found, of which mortality due to bladder cancer was 199,922 cases worldwide (WHO, 2019a).

The incidence was highest in Asia (36%), followed by Europe (35.9%) and the Americas (16.7%). Mortality from bladder cancer is also in the same order, occurring mostly in Asia (42.4%), followed by Europe (32.5%), and the Americas (10.1%). Data in Indonesia according to GLOBOCAN 2020 states that 2.17% of all malignancies are bladder cancer cases with 6,716 new cases and 3,375 deaths in 2018 (WHO, 2019b).

MIBC occurs in approximately 25-30% of patients with bladder cancer (Zhang et al., 2020), and is an aggressive malignancy with a high risk of organ spread compared to non-muscle invasive bladder cancer (NMIBC) (Zhu et al., 2019).

Patients with MIBC are reported to have a significantly lower 5-year survival compared to NMIBC, 69% versus 95% (Al-Husseini et al., 2019; Zhu et al., 2019), which can be as low as 5.5% at the pT4 stage (van Kessel et al., 2016). Approximately 50% of patients will develop metastatic disease within 2 years, with a median survival time of only 15% (Kaiser et al., 2018).

The link between inflammation and carcinogenesis has been increasingly studied, where systemic inflammation can inhibit apoptosis and stimulate tumor proliferation, invasion, and angiogenesis (Yilmaz et al., 2020). The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) are some of the markers of inflammatory status and immune conditions that show promising roles in predicting tumor progression, metastasis, and prognosis of malignancies (Hai et al, 2021; Ekin et al. 2015; Kaiser et al. 2018; Wu et al. 2020; Zhang et al. 2020).

Recent research on the role of NLR by Zhang, et al. (2021) in China also showed that dynamic changes in postoperative NLR values are potential markers for bladder cancer recurrence detection, with patients with elevated NLR after surgery showing a higher risk of recurrence.

Platelet to lymphocyte ratio (PLR) has been previously recognized as a marker of inflammation, infection, and malignancy (Ekin et al., 2015). A 2019 meta-analysis by Wang et al. found that pretreatment PLR values can be a predictive biomarker for poor prognosis of bladder cancer patients. The study, which included approximately 3033 patients, reported that increased PLR was significantly associated with poor overall survival (HR 1.26; 95% CI 1.03-1.54; p-value 0.026).

Lymphocyte-to-monocyte ratio (LMR) has recently been increasingly studied as one of the biomarkers of poor prognosis of malignancy patients, where its easy availability and low cost are also advantages that continue to attract attention (Hai et al., 2021). A retrospective study in China from 2004 to 2017 showed 347 patients with bladder cancer who had high LMR levels before radical cystectomy had better overall survival (Hai et al., 2021).

Until now, there are still no studies that examine the potential of NLR, PLR, and LMR together as markers of prognosis for outcomes of patients with muscle-invasive bladder cancer in Indonesia. In addition, there is still controversy regarding the role of the three markers from the studies mentioned above.

METHODS

This type of study is a retrospective cohort study to prove the value of NLR, PLR, and LMR as independent predictors in predicting outcomes in patients with MIBC.

The population in this study were patients with MIBC, the diagnosis was made by histopathological examination which was confirmed after the standard therapeutic procedure, which is radical cystectomy with or without therapy (Neoadjuvant chemotherapy / adjuvant chemotherapy) who underwent a series of routine follow-ups at the Urology Surgery Polyclinic of Prof. Dr. I.G.N.G. Ngoerah Hospital. The sample in this study was selected using consecutive sampling by selecting subjects who met the research criteria in the period January 2015 to December 2021 involved 50 MIBC patients who have undergone curative procedures. The inclusion criteria in this study are 1) Patients who have undergone definitive surgery for MIBC (patients diagnosed with muscle-invasive bladder cancer who have undergone the standardized therapeutic procedure of radical cystectomy). 2) Have complete blood data before therapy. 3) Have 1 year of life and death data. 4) Patient age > 18 years. The exclusion criteria in this study are 1) Patients are suffering from immunodeficiency diseases that can affect NLR, PLR, and LMR levels. 2) Patients refused to take interview data or laboratory data after inform consent was given. Data analysis was performed using SPSS for Windows version 25.0 software. The statistical analysis included univariate analysis, bivariate analysis, and multivariate analysis.

RESULTS
Characteristics of the study

This study successfully obtained a total of 178 bladder cancer patients from medical record data from 2015 to 2021, and 131 patients were MIBC (73%). Of all MIBC patients, 52 patients underwent radical cystectomy (39%). Of this group of MIBC patients who underwent radical cystectomy, 50 patients met the inclusion criteria. Of these patients who met the inclusion criteria, 9 patients (18%) died and 41 patients (82%) lived. Patients had a mean age of 58.02 ± 10.5 years, urothelial carcinoma type (80%), male gender (86%), stage T4 (50%), stage N0 (52%), and stage M0 (72%). Respondents' characteristics were described based on age, gender, tumor stage (TNM), history of systemic disease, history of chemotherapy administration, tumor type, NLR, PLR, and LMR. The result is presented in Table 1.

TABLE 1: Characteristics of Study Subjects.

Variable	Mortality	
	Yes (N=9)	No (N=41)
Age (years), mean ± SD	**56,3 ± 5,05**	**58,3±11,4**
Age group, n (%)		
≤65 years	6 (66,7)	23 (56,1)
>65 years	3 (33,3)	18 (43,9)
Gender, n (%)		
Male	9 (100)	34 (82,9)
Female	0 (0)	7 (17,07)
Stage T, n (%)		
2	5 (55,6)	17 (41,5)
3	0 (0)	3 (7,3)
4	4 (44,4)	21 (51,2)
Stage N, n (%)		
0	4 (44,4)	22 (53,7)
1	4 (44,4)	12 (29,3)
2	1 (11,2)	7 (17,1)
Stage M, n (%)		
0	4 (44,4)	32 (78,0)
1	5 (55,6)	9 (22,0)
Systemic Disease		
Present	3 (33,3)	14 (34,1)
None	6 (66,7)	27 (65,9)
Chemotherapy		
Neoadjuvant	5 (55,6)	24 (58,5)
Adjuvant	4 (44,4)	17 (41,5)
Tumor type		
Urothelial carcinoma	7 (77,7)	33 (80,4)
Squamous cell carcinoma	1 (11,1)	6 (14,63)
Adenocarcinoma	1 (11,1)	2 (4,87)

ROC Analysis of NLR, PLR, and LMR as Predictors of Mortality in Muscle Invasive Bladder Cancer Patients

ROC curve analysis and depiction (Figure 1) were used to obtain the cut-off values of NLR, PLR, and LMR for mortality of MIBC patients. The cut-off values obtained can be seen in Table 2.
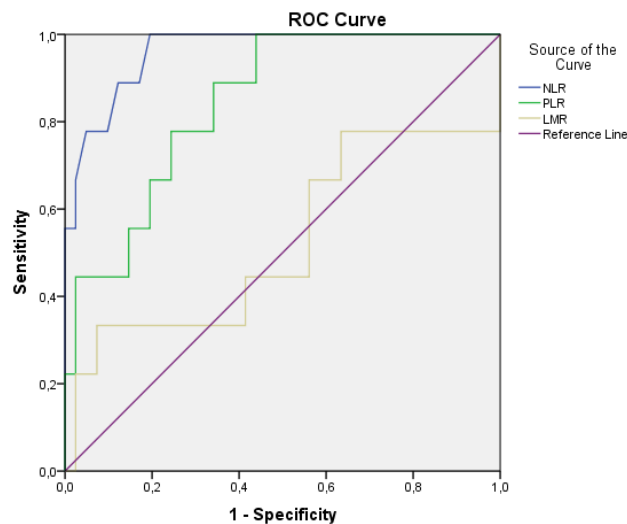

FIGURE 1: Receiver operating characteristic (ROC) curves of NLR, PLR, and LMR.

TABLE 2: ROC Analysis Results.

Variable	AUC	P-value	Cut-off value	Sensitivity	Specificity
NLR	0,961	<0,001	4,74	100%	78%
PLR	0,843	0,001	163,56	78%	76%
LMR	0,523	0,830	1,89	66%	44%

Relationship of NLR, PLR, and LMR with Mortality of Muscle Invasive Bladder Cancer Patients

The chi-square test showed a significant association between NLR and MIBC mortality (OR=24.8; 95%CI=2.75-223.2; p=0.001) and between PLR and MIBC mortality (OR=10.8; 95%CI=1.93-60.9; p=0.004). There was no relationship between LMR and MIBC mortality (p=0.561).

TABLE 3: Relationship between NLR, PLR, and LMR with Mortality of Muscle Invasive Bladder Cancer Patients.

Variable	Mortality		OR	95%CI	p
	Yes	No			
NLR					
≥4,74	8 (88,9%)	10 (24,4%)	24,8	2,754-223,297	0,001
<4,74	1 (11,1%)	31 (75,6%)			
PLR					
≥163,56	7 (77,8%)	10 (24,4%)	10,850	1,932-60,930	0,004
<163,56	2 (22,2%)	31 (75,6%)			
LMR					
≥1,89	6 (66,7%)	23 (56,1%)	1,565	0,343-7,135	0,561
<1,89	3 (33,3%)	18 (43,9%)			

Survival Analysis of NLR, PLR, and LMR on Mortality of Muscle Invasive Bladder Cancer Patients

The results of the analysis of survival based on Kaplan-Meier curves showed that MIBC patients who had high NLR levels had an overall survival rate of 55.6% while MIBC patients who had low NLR levels had an overall survival of 96.9% (p = 0.001).
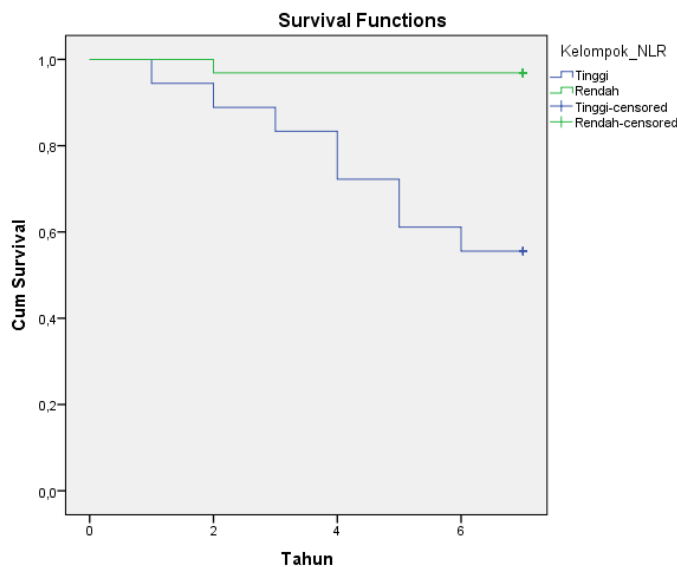

FIGURE 2: Kaplan-Meier survival curves based on NLR level.

The results of the survival analysis based on the Kaplan-Meier curve showed that MIBC patients who had high PLR levels had an overall survival rate of 58.8% while MIBC patients who had low PLR levels had an overall survival of 93.9% (p=0.002).
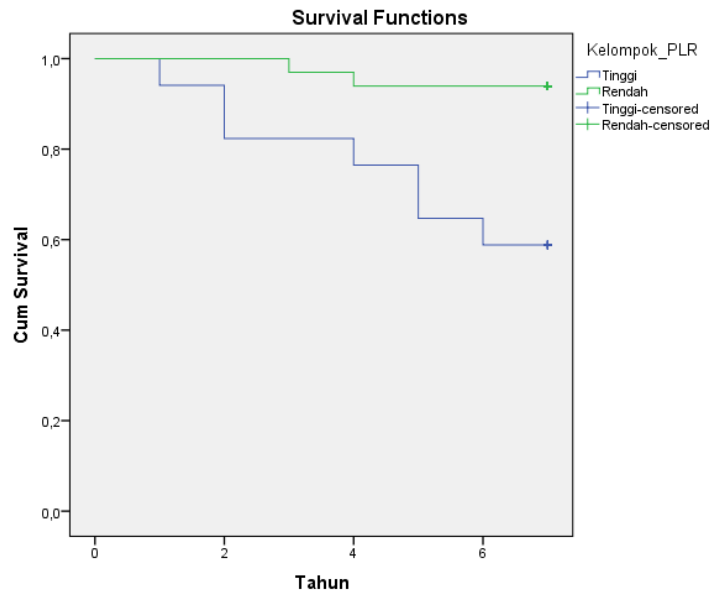
FIGURE 3: Kaplan Meier Survival Curve based on PLR level.

The results of the survival analysis based on the Kaplan-Meier curve showed that MIBC patients who had high LMR levels had an overall survival rate of 79.3% while MIBC patients who had low LMR levels had an overall survival of 85.7% (p=0.607).
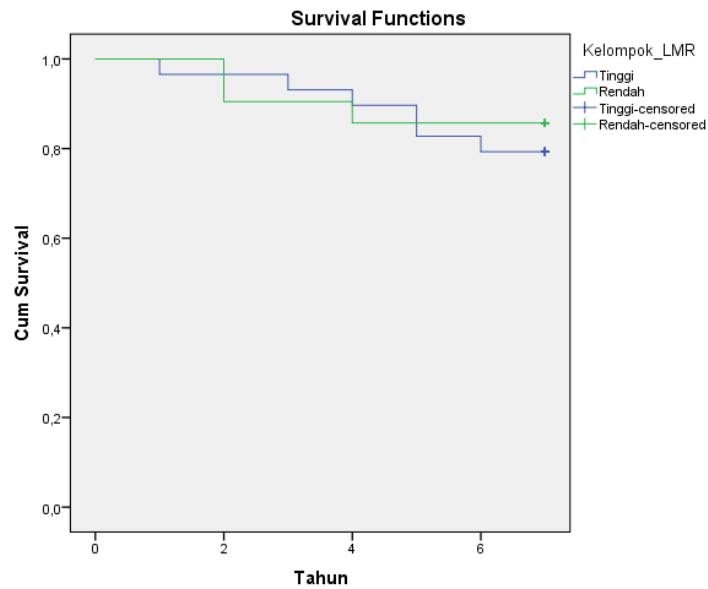

FIGURE 4: Kaplan Meier Survival Curve based on LMR level.

Multivariate analysis with the Cox regression test showed that high NLR was an independent predictor of MIBC mortality after confounding variables were controlled (Table 4).

TABLE 4: Multivariate Analysis Results.

Variable	B	Adj (OR)	95%CI	P value
NLR (high)	3,322	27,728	1,443-532,756	0,028
PLR (high)	2,413	11,116	0,778-160,166	0,076
LMR (high)	2,179	8,836	0,604-129,259	0,111
Age (<65 years)	-0,671	0,511	0,058-4,467	0,544
Gender (male)	2,292	9,896	0,256-382,576	0,219
Stage T (T2)	-1,399	0,247	0,014-4,321	0,338
Stage N (N0)	-0,698	0,498	0,033-7,451	0,613
Stage M (M0)	-1,348	0,260	0,012-5,530	0,388
Chemotherapy type (*neoadjuvant*)	-0,463	0,629	0,008-47,971	0,834
Tumor type (urothelial)	2,627	13,834	0,478-399,942	0,126
Systemic disease (present)	-0,369	0,691	0,059-8,060	0,768

DISCUSSION

NLR as a predictor of worse outcomes in MIBC patients

This study shows that high NLR (≥4.74) can be used as a predictor of 5-year mortality of MIBC patients. The results of this study are consistent with a study by Kaiser et al. (2018) in Canada of a total of 376 MIBC patients during a median follow-up of 22 months which showed that consistently high NLR values (NLR>3) had significantly lower disease-free survival (DSS) (12.6 months) compared to patients with consistently low NLR (34.8 months) (p-value = 0.0025). The study also noted that the median overall survival (OS) of patients with consistently high NLR was significantly lower (19.4 months) compared to patients who had consistently low NLR (44 months) (p-value = 0.0011) (Kaiser et al., 2018).

The same results were confirmed by another study, namely by Wu, et al. (2020) which concluded that in muscle-invasive bladder cancer patients with bladder-sparing therapy, adequate doses of combined chemoradiotherapy with low NLR were found to be associated with better progression-free survival (PFS). This study of 193 patients in Taiwan found that high pre-chemotherapy NLR values (≥3) were significantly associated with lower complete response (CR) rates, increased risk of locoregional recurrence, and decreased bladder-preservation survival. This study suggests the use of NLR as a clinical marker for MIBC prognosis and a guideline for management options in patients with MIBC.

Another study that also confirmed high NLR as a prognostic factor in predicting low clinical response to neoadjuvant chemotherapy and lower DSS and OS was also confirmed by Black, et al. (2019). Recent research on the role of NLR by Zhang, et al. (2021) in China also showed that dynamic changes in postoperative NLR values are potential markers for bladder cancer recurrence detection, with patients with elevated NLR after surgery showing a higher risk of recurrence.

Slightly different study results were shown in a study at a military hospital in China (Zhang et al., 2020) which examined a total of 202 patients with muscle-invasive bladder cancer (MIBC) who underwent radical cystectomy. This study showed that high NLR values (≥2.42) were associated with poor OS (p-value = 0.034), but not PFS and cancer-specific survival (CSS). Another study by Yilmaz, et al. (2020) also showed inconsistent results on the role of NLR markers in predicting the prognosis of cancer patients with MIBC. The study found that indeed PFS and OS were lower in patients with high NLR (NLR≥2.77) in bivariate analysis. However, after multivariate analysis, NLR could not provide unequivocal results as an independent prognostic factor. (Zhang et al., 2021) This difference may be due to the NLR cut-off value that is different from other studies. In addition, the cause of inconsistency in the results of the study is also thought to be due to differences in race, living environment, tumor type, tumor heterogeneity, choice of therapy, or internal factors from patients such as age and immune status.

PLR as a predictor of worse outcomes in MIBC patients

This study shows that high PLR (≥163.56) can be used as a predictor of 5-year mortality of MIBC patients. This result is in accordance with a study by Wang et al. in 2019 which found that pretreatment PLR value is a predictive biomarker for poor prognosis of bladder cancer patients. The study, which included approximately 223 patients over 8 years, reported that an increase in PLR (cutoff 164.7) was significantly associated with poor overall survival (HR 1.26; 95% CI 1.03-1.54; p-value 0.026) (Wang et al., 2019). The results of this study differ from the study of Rajwa et al (2018) in 144 patients which showed that only NLR was statistically significant in multivariate analysis while PLR was not. The cutoff PLR used was 128.4 (Rajwa et al., 2018).

Studies on PLR in bladder cancer are scarce, and its prognostic role remains controversial. A recent meta-analysis consisting of only 3 low-quality studies showed that increased PLR was negatively associated with OS of various types of urological cancers, except bladder cancer (Li et al., 2017). This may be due to the lack of sufficient high-quality studies to draw a conclusive answer. Therefore, to further evaluate the role of PLR, more bladder cancer cohorts are needed. PLR is studied in general as a marker of inflammation, infection, or malignancy (Ekin et al., 2015). The interaction of platelets with leukocytes and endothelial cells will lead to the release of inflammatory factors, which trigger monocyte adhesion and transmigration. Thus, platelet levels reflect the status of inflammation, thrombosis, and atherogenesis. In addition, decreased lymphocyte counts are also significantly associated with increased mortality. The combination of increased platelet count and decreased lymphocyte count leads to increased PLR, which can predict poor outcomes in inflammatory conditions (Ye et al., 2019).

The presence of platelets associated with cancer deposits has also been recognized. Tumors can activate platelets by producing platelet activators and mediators or by direct contact with tumor cell membranes. Conversely, platelets induce tumor angiogenesis by secreting proangiogenetic cytokines such as vascular endothelial growth factor (VEGF) and angiopoietin-1 (Wang et al., 2019). Just like NLR, PLR can be obtained from a complete blood test that can be found in various healthcare facilities (Balta and Otzurk, 2015; Ekin et al., 2015).

LMR as a predictor of worse outcomes in MIBC patients

This study showed no relationship between LMR and MIBC prognosis. This result is different from a retrospective study in China from 2004 to 2017 which showed bladder cancer patients who had high LMR levels before radical cystectomy had a better overall survival rate (Hai et al., 2021).

Another retrospective study comparing NLR, PLR, and LMR as predictive biomarkers in bladder cancer by Adamkiewicz et al. in 2021 concluded that LMR is a biomarker for poor prognosis of patients with bladder cancer whose ability to outperform the other two biomarkers. The three markers were indeed found to have independent prognostic ability in bladder cancer, although the prognostic value of LMR was higher in predicting poor clinical outcomes.

Another study by Yildiz et al, in 2021 also provided results that strengthen the attractiveness of LMR to become a biomarker that is cost-effective, widely available, and non-invasive in predicting the poor prognosis of bladder cancer patients. The study with an average follow-up of 11 ± 6 months found that although NLR statistically significantly showed an association with recurrence (p-value 0.019) in bivariate survival analysis, LMR values showed more consistent results with significant results associated with bladder cancer recurrence in both bivariate and multivariate analysis (p-value 0.021; p-value 0.022, respectively).

Age is a widely studied prognosis factor for bladder cancer patients. This study found that the age of 65 years was not a predictor of poor outcomes in patients with muscle-invasive bladder cancer. This result is consistent with a previous study of 163 patients with muscle-invasive bladder cancer which showed that age was not an independent predictor of disease-specific survival (Schrier et al., 2004). Another study in 225 patients with muscle-invasion bladder cancer in Turkey also reported that age was not a prognostic factor of cancer-specific survival at 2, 3, and 5 years (Turkolmez et al., 2007). Different results obtained in a study by Lin et al. (2023) based on patient data from 2004-2015 showed that patients aged 75 years had a lower OS than patients aged 54 years with an increased risk of death of 5.36 times higher. Another study by Janisch et al. (2019) reported that age >67 years was a predictor for disease recurrence and cancer-specificity and higher overall mortality in bladder cancer patients. However, both studies were not specific to bladder cancer with muscle invasion and used a higher cut-off age. Age is a consideration in the choice of therapy. About one-fifth of bladder cancer patients with muscle invasion aged 75 years did not receive therapy due to poor performance status and decreased renal function. Median OS was generally found to be lower in patients who did not receive therapy (Van Hoogstraten, et al., 2022).

This study did not show any difference in prognosis based on TNM stage. Research on the relationship between TNM stage and prognosis of bladder cancer patients is still inconclusive. Research by Schrier et al (2004) reported that patients who had primary tumors (pT2/T3) without lymphonodi metastasis or distant metastasis had better disease-specific survival. The presence of lymphonodi and distant metastases increased the risk of disease-specific mortality, respectively by 2.07 and 6.77

times higher than primary tumors without metastases (Schrier et al., 2004). A study by Turkolmez et al. (2007) reported that tumor size (T stage) and distant metastasis (M) were significant prognostic factors independent of cancer-specific survival. However, the presence of lymphovascular spread did not act as a prognostic factor for outcomes in patients with muscle-invasive bladder cancer. The involvement of T, N, and M stages in bladder cancer patient outcomes also varies depending on the duration of survival observed. Larger tumor size ($\geq$pT3) was associated with worse 1- and 2-year survival, but no difference was found for 3-, 4- and 5-year survival. Positive lymphonodies were also reported to be associated with worse 1-, 2-, and 3-year survival, but not significantly different for 4- and 5-year survival after radical cystectomy (Kang et al., 2015).

The type of chemotherapy given (neoadjuvant and adjuvant chemotherapy) is not a prognostic factor for survival in patients with bladder cancer (Kang et al., 2015). A Turkish study reported that the survival of patients receiving neoadjuvant and adjuvant chemotherapy did not differ significantly. Compared to the type of chemotherapy, patient prognosis is more related to the response to chemotherapy. A better prognosis was found in the group of patients who responded to therapy, either NAC or adjuvant chemotherapy (Sekmek et al., 2023). Patients who received trimodal therapy (TMT) with transurethral tumor resection followed by chemotherapy had similar survival compared to patients who underwent radical cystectomy and neoadjuvant chemotherapy (RC-NAC) in the group of patients aged $\geq$65 years. Patient survival was observed to be lower in the group receiving TMT compared to RC-NAC in patients <65 years of age. This suggests that more invasive approaches and NAC administration may be considered in younger age groups (Kumar et al., 2021). A meta-analysis also proved that adjuvant chemotherapy improves recurrence-free survival, locoregional recurrence-free survival, and metastasis-free survival in MIBC (Burdett et al., 2021).

Different results were also reported in several previous studies where NAC administration was associated with a better prognosis than adjuvant chemotherapy (Sawasdee et al., 2022; Choi et al., 2022). Neoadjuvant chemotherapy has the advantage of reducing cancer cell shedding and implantation while radical cystectomy can eradicate micrometastasis. However, NAC also has the disadvantages of toxicity and delay in definitive surgery, so its use still requires clinical judgment (Sawasdee et al., 2022).

A study by Prijovic et al. (2023) compared the prognosis of bladder cancer patients between groups of pure urothelial carcinoma type and other histologic variants. Most of the other histology variants were squamous type (46%) followed by micropapillary, glandular, lyphoepithelioma, sarcomatoid, plasmacytoid, and neuroendocrine differentiation.

The results showed that other histological variants were associated with more advanced tumor stages and lower OS compared to pure urothelial carcinoma patients (Prijovic et al., 2023). When adjusted for stage, oncologic outcomes were generally similar based on the histologic variant, except for pure squamous cell carcinoma and signet ring cell carcinoma. The overall survival (OS) of the signet-ring variant after radical cystectomy was generally inferior to pure urothelial carcinoma (Processali et al., 2020). This study differentiated the group into urothelial carcinoma and non-urothelial carcinoma types, where this histology type was not associated with the survival of patients with muscle invasion bladder cancer.

CONCLUSIONS

Based on the research and discussion, it can be concluded that:

- High NLR is an independent predictor of poor outcomes in muscle-invasive bladder cancer patients.
- High PLR is a predictor of poor outcomes in muscle-invasive bladder cancer patients.
- Low LMR is not a predictor of poor outcomes in muscle-invasive bladder cancer patients.
- High NLR and PLR may indicate poor overall survival in muscle-invasive bladder cancer patients.

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