

Absolute lymphocyte count as a predictor of mortality and readmission in heart failure hospitalization

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ABSTRACT

Background: There is renewed interest in pursuing frugal and readily available laboratory markers to predict mortality and readmission in heart failure. We aim to determine the relationship between absolute lymphocyte count (ALC) and clinical outcomes in patients with heart failure hospitalization.

Methods: This was a retrospective cohort study of patients with heart failure. Patients were divided into two groups based on ALC, less than or equal to 1500 cells/mm³ and > 1500 cells/mm³. The primary outcome was all-cause mortality. We did subgroup analysis based on ejection fraction and studied the association between ALC categories and clinical outcomes. Both ALC groups are matched by propensity score, outcomes were analyzed by Cox regression, and estimates are presented in hazard ratios (HR) and 95% confidence intervals (CI).

Results: We included 1029 patients in the pre-matched cohort and 766 patients in the propensity-score matched cohort. The median age was 64 years (IQR, 54–75), and 60.78% were male. In the matched cohort, ALC less than or equal to 1500 cells/mm³ had a higher risk of mortality compared with ALC > 1500 cells/mm³ (HR 1.51, 95% CI: 1.17–1.95; P = 0.002). These results were reproducible in subgroups of heart failure. When ALC was divided into four groups based on their levels, the lowest group of ALC had the highest risk of mortality.

Conclusions: In patients with heart failure and both subgroups, ALC less than or equal to 1500 cells/mm³ had a higher risk of mortality. Patients in lower groups of the ALC categories had a higher risk of mortality.

1. Introduction

Heart failure (HF) is a complex clinical syndrome associated with high morbidity and mortality. There is an increasing prevalence of HF due to the development of mortality-reducing therapies over the last 30 years. However, heart failure is still the most common cause of hospital readmissions in the United States [1,2]. In patients hospitalized for acute

heart failure, one-year mortality and readmission rate are 17.4% and 43.9%, respectively [1].

Various risk models from the trials, registries, and cohort studies have consistently demonstrated age, blood pressure, hemoglobin, sodium concentration, renal function, pro-brain natriuretic peptide (pro-BNP), left ventricular ejection fraction, no beta-blocker, and the dose of diuretic at discharge associated with mortality or readmission prediction

Abbreviations: ALC, absolute lymphocyte count; HR, hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LVEF, left ventricular ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; PSM, propensity-score matching.

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[3]. In recent years, there is renewed interest in pursuing frugal and readily available laboratory markers to predict mortality and hospital readmission in HF. Lymphopenia in HF was first described in 1960 [4]. Subsequently, literature studied the role of neutrophil-to-lymphocyte ratio (NLR) [5-7], platelet-to-neutrophil ratio (PNR) [8-10], monocyte-lymphocyte ratio and lymphocyte percentage [11,12] as potential independent predictors of mortality. However, these indices can be altered in conditions that affect neutrophils and platelets. Acute infection or stress can easily alter neutrophil count, while its effect on lymphocytes is minimal. Lymphocyte percentage is a proportional representation of total white blood cell count, and hence it can be affected with change in other cell lineages. Hence, we preferred absolute lymphocyte count (ALC) over other lymphocyte markers. Previous studies in heart failure patients have shown an association between lymphocyte count and mortality [13,14], but there are very few studies

that assessed an association between ALC grading and mortality, [14] and or association between ALC and readmission. We aimed to fill this void by assessing ALC's role in predicting mortality, all-cause readmission, cardiac readmission, and a composite of mortality or readmission at 30 days and 6 months in patients with acute heart failure.

1.1. Methods

1.1.1. Data source and study population

This is a single-center retrospective cohort study of acute heart failure hospitalization in the New York City. We collected information on consecutive patients hospitalized from January 2005 to December 2018, as per our inclusion and exclusion criteria mentioned below. The institutional review boards approved this study and permitted a waiver of informed consent from the study participants due to the retrospective

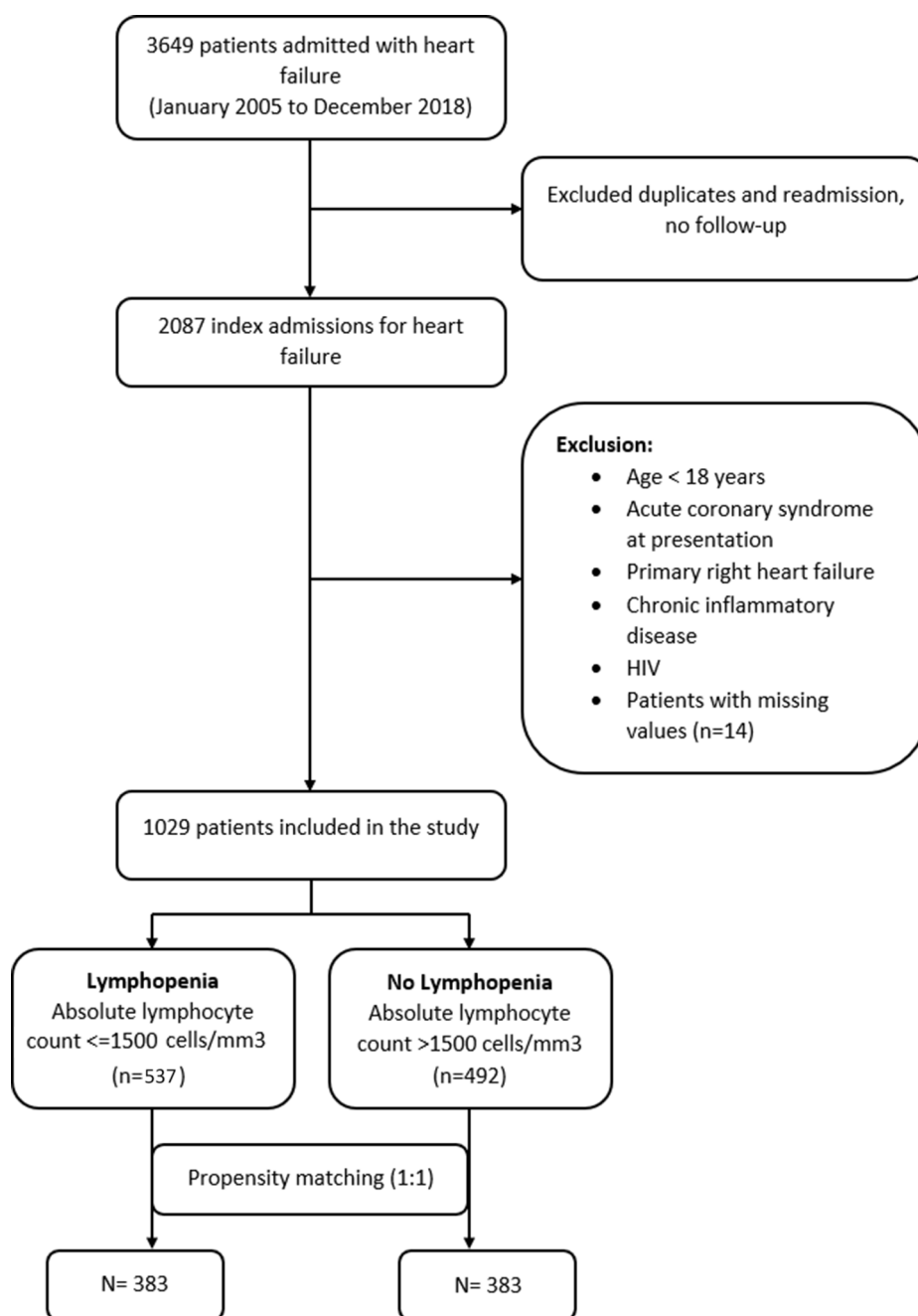


Fig. 1. Patient selection.

nature of the study. Acute heart failure was defined according to the guideline criteria as acute onset (or worsening) of signs and symptoms of heart failure needing urgent hospitalization and intravenous treatment. [15] The exclusion criteria were: age < 18 years old, acute coronary syndrome at the time of presentation, primary right-sided heart failure, comorbidities that are known to affect the lymphocyte count, such as active infection, chronic inflammatory disease, chronic corticosteroid use in the past three months, and human immunodeficiency virus. The infection diagnosis was based on clinical information from the notes as documented by the admitting physician or laboratory criteria such as lactic acid and C-reactive protein suggestive of infection. For patients with previous heart failure, the first admission to the hospital was considered an index event. Fig. 1 summarizes patient selection.

We reviewed and collected demographic, clinical, laboratory, medication information, and outcomes from the electronic medical records between June to October 2020. The definitions of all extracted data and outcomes were recorded separately and checked by two authors (M.M. and T.K.). All the data extraction was done manually, which was verified by a second physician. Any disparity was resolved by consulting the primary investigator. Patient confidentiality was protected by de-identification, and the data were stored in a locked, password-protected data storage device.

1.1.2. Primary predictor and outcomes

Our primary predictor was ALC, obtained at admission. ALC was measured by Sysmex automated hematology analyzer XN-10. We divided ALC into two groups, one with $ALC \leq 1500$ cells/mm³ and the other > 1500 cells/mm³ (comparison group) based on median value obtained from our study as well as from a previous study. [16] We further divided ALC into 4 groups; Group A > 2000 cells/mm³ (comparison group), Group B 1501–2000 cells/mm³, Group C 1001–1500 cells/mm³, and Group D ≤ 1000 cells/mm³. This division was based on our IQR (interquartile range). Our primary outcome was all-cause mortality. Secondary outcomes were all-cause readmission, cardiac readmission, and a composite of readmission or mortality at 30 days and 6 months. All the outcomes were collected in ‘time to event’ format. They were defined as the time from discharge date to the date of occurrence of events. The clinical outcomes were determined by electronic medical records from all the hospitals of the organization. The occurrence of death was determined from the medical record, telephonic call, or social security death index master file by two-point identifier, name, and birth date. Cardiac readmission was defined as readmission due to heart failure, myocardial infarction, and/or arrhythmias as a primary discharge diagnosis. We performed a subgroup analysis by left ventricular ejection fraction (LVEF). Patients with $LVEF \leq 40\%$ were grouped under heart failure with reduced ejection fraction (HFrEF), and with $LVEF > 40\%$ were grouped under heart failure with preserved ejection fraction (HFpEF).

1.1.3. Statistical analysis

Baseline characteristics of both groups of ALC were expressed using descriptive statistics. The continuous variables were demonstrated as median with interquartile range (IQR). Categorical variables were presented in frequency and proportion. The Mann-Whitney-Wilcoxon tests were applied to compare continuous variables. Fisher’s exact test or Pearson’s Chi² tests were implemented to compare categorical variables. The Kaplan-Meier curves were used to demonstrate the rate of events in each group; the comparison between the two groups was calculated with the log-rank test. For death, censoring was applied at last objective evidence of survival available. For readmission, censoring was applied at six months. We built a multivariate cox-proportional hazard model to determine the hazard ratio (HR) and 95% confidence interval (CI) for the lymphopenia group compared with the group with normal ALC defined as $ALC > 1500$ cells/mm³. The final model was built by both the forward selection and backward elimination method. A p-value of 0.20 was set as a cut-off for the variable to include in the final multivariable

model. The variables mentioned in the literature that can possibly be associated with the outcomes were also included in the final model. In the final model, we included age, gender, race, ejection fraction, coronary artery disease, stroke, cancer, hypertension, diabetes, atrial fibrillation, chronic lung disease, body mass index, pro-BNP, hemoglobin, sodium, glomerular filtration rate, albumin, and medications such as loop diuretic, beta blocker, ACE inhibitors or ARB, spironolactone, digoxin, aspirin/clopidogrel, warfarin/other anticoagulation, and statins. We also utilized a propensity-score matching methodology (PSM) to match patients with $ALC \leq 1500$ cells/mm³ to those with > 1500 cells/mm³ at a 1:1 ratio. The nearest neighbor technique was adopted to match each patient in two groups by calculating propensity-score, with a caliper of 0.2. The variables used to calculate propensity-score are similar to those used in the multivariable model. After matching, we ran a univariate cox-proportional hazard analysis to determine the HR with 95% CI. We applied the test for proportionality assumption based on Schoenfeld Residuals. Missing data were not imputed. A p value < 0.05 was considered statistically significant. Statistical analysis was performed using STATA version 16.1 (StataCorp LLC).

1.2. Results

1.2.1. Baseline characteristics

We performed a retrospective cohort study of 1029 patients. The median follow-up period was 860 days (2.35 years). The median age was 64 years (IQR, 54–75), 61% (626) were males and 40.1% (413) were African American. Baseline demographic characteristics, laboratory parameters at admission, echocardiographic features, and discharge medications included in the study are in Table 1. As demonstrated in Table 1, patients with $ALC \leq 1500$ cells/mm³ compared with patients with $ALC > 1500$ cells/mm³ were older (67 vs. 62 years; $P < 0.001$), had a lower median blood pressure (99.33 vs. 102.67 mmHg; $P = 0.011$), lower median body mass index (27.8 vs 30.3 kg/m²; $P < 0.001$), higher median pro-BNP levels (7924 vs. 3574 picograms/milliliter; $P < 0.001$), lower hemoglobin levels (11.6 vs. 12.3 g/dL; $P < 0.001$), and lower glomerular filtration rate (57.58 vs. 64.62 ml/min; $P = 0.013$). Other baseline characteristics were comparable in both groups. Baseline characteristics between the two groups after the PSM method are extrapolated in Table 2. The matched cohort had 766 patients based on 25 matched variables. The distribution of propensity-score between two groups and balance of covariates between two cohorts after matching are demonstrated in Supplemental Figure 1, Figure 2.

1.2.2. Primary outcome (Mortality) (Fig. 2)

Out of 1029 eligible patients, 137 (27.85%) patients died in cohort of $ALC > 1500$ cells/mm³ compared with 199 (36.99%) patients in cohort of $ALC < 1500$ cells/mm³ ($P = 0.002$) (Table 1). Using the PSM model, patients with $ALC < 1500$ were associated with increased hazard of mortality (HR 1.51, 95% CI: 1.17–1.95; $P = 0.002$). These results were similar to the results obtained with univariate and multivariate analysis (Supplemental Table 1).

1.2.3. Secondary outcomes (Fig. 2)

In the cohort of $ALC \leq 1500$, 46.10% (248) patients were readmitted within 6 months compared with 33.33% (164) in the cohort of $ALC > 1500$ ($P < 0.0001$) (Table 1). In the PSM method, the analysis showed a higher hazard ratio for readmission in the cohort of $ALC < 1500$ cells/mm³ at 30 days and 6 months (30-day HR 1.49, 95% CI: 1.02–2.17, $P = 0.039$; 6-month HR 1.54, 95% CI: 1.23–1.95, $P < 0.001$). The proportionality assumption was not violated (global test $P = 0.47$).

In the cohort of $ALC \leq 1500$, 33.27% (179) patients had cardiac readmission within 6 months compared with 24.8% (122) in the cohort of $ALC > 1500$ ($P = 0.003$) (Table 1). Cox analysis and PSM method showed a similar rate of cardiac readmission at 30 days between two groups; however, at 6 months, $ALC \leq 1500$ had a higher risk of cardiac readmission (adjusted HR 1.40, 95% CI: 1.10–1.79, $P = 0.007$, by PSM HR

Table 1
Baseline demographic and clinical characteristics of patients by absolute lymphocyte count before matching.

	All patients (N = 1029)	No Lymphopenia (ALC > 1500 cells/mm ³) (N = 492)	Lymphopenia (ALC ≤ 1500 cells/mm ³) (N = 537)	P-value
Demographic				
Age (years), median (IQR)	64 (54 – 75)	62 (52.5 – 72)	67 (56 – 78)	<0.001
Male, n (%)	626 (60.8)	294 (59.8)	332 (61.7)	0.521
White, n (%)	86 (8.4)	39 (7.9)	47 (8.7)	0.083
Black, n (%)	362 (35.2)	190 (38.6)	172 (32)	
Hispanic, n (%)	582 (56.5)	263 (53.5)	319 (59.3)	
Comorbidities				
Hypertension, n (%)	888 (86.2)	426 (86.6)	462 (85.9)	0.741
Diabetes, n (%)	526 (51.1)	260 (52.9)	266 (49.4)	0.275
CAD, n (%)	302 (29.4)	136 (27.7)	166 (31)	0.25
Stroke, n (%)	93 (9)	44 (8.9)	49 (9.1)	0.927
Cancer, n (%)	87 (8.5)	44 (8.9)	43 (8)	0.584
Atrial fibrillation, n (%)	247 (24)	115 (23.4)	132 (24.5)	0.663
Chronic lung disease, n (%)	193 (18.7)	87 (17.7)	106 (19.7)	0.407
Parameters on admission				
MAP (mm Hg), median (IQR)	101 (89.7 – 115.3)	102.67 (90.7 – 117.3)	99.33 (89.3 – 113)	0.011
BMI, median (IQR)	28.9 (24.8–35.4)	30.3 (25.5–37)	27.8 (24.3–33.7)	<0.001
Pro-BNP (pg/ml), median (IQR)	5179 (2157 – 12712)	3574 (1553 – 8382)	7924 (2614 – 17052)	<0.001
Hb (g/dL), median (IQR)	11.9 (10.5 – 13.4)	12.3 (11–13.7)	11.6 (10.1–13)	<0.001
GFR (ml/min/m ²), median (IQR)	61.92 (37.9 – 85.5)	64.62 (42.3–86.7)	57.58 (35.3–85)	0.013
Sodium (mEq/L), median (IQR)	139 (137 – 141)	139 (137–142)	139 (136–141)	0.008
Echocardiographic features				
EF > 40%, n (%)	384 (37.3)	193 (39.2)	191 (35.5)	0.217
LAD (cm), median (IQR)	4.3 (4 – 4.8)	4.3 (4 – 4.8)	4.4 (4 – 4.9)	0.014
LVIDD (cm), median (IQR)	5.5 (4.9 – 6.1)	5.5 (4.9 – 6)	5.5 (5 – 6.1)	0.99
Discharge medications				
Loop diuretics, n (%)	815 (79.2)	382 (77.6)	433 (80.6)	0.238
Beta blocker, n (%)	821 (79.7)	399 (81.1)	422 (78.4)	0.289
ACE inhibitors/ARB, n (%)	766 (74.4)	372 (75.6)	394 (73.2)	0.383
CCB, n (%)	278 (27)	124 (25.2)	154 (28.6)	0.217
Spirolactone, n (%)	188 (18.3)	83 (16.9)	105 (19.5)	0.272
Digoxin, n (%)	282 (27.4)	132 (26.8)	150 (27.9)	0.705
Aspirin/clopidogrel, n (%)	812 (78.8)	404 (82.1)	408 (75.8)	0.014
Anticoagulation, n (%)	185 (18)	79 (16.1)	106 (19.7)	0.128
Statin, n (%)	668 (64.9)	341 (69.3)	327 (60.8)	0.004
Outcomes				
Death, n (%)	336 (32.6)	137 (27.9)	199 (37)	0.002
All-cause readmission, n (%)	412 (40)	164 (33.3)	248 (46.1)	<0.001
Cardiac readmission, n (%)	301 (29.22)	122 (24.80)	179 (33.3)	0.003
Death or readmission, n (%)	575 (55.8)	239 (48.6)	336 (62.5)	<0.001

Abbreviations: ACE – angiotensin converting enzyme, ALC – absolute lymphocyte count, ARB – angiotensin receptor blocker, BMI – body mass index, CAD – coronary artery disease, EF – ejection fraction, GFR – glomerular filtration rate, Hb – hemoglobin, IQR – interquartile range, LAD – left atrial diameter, LVIDD – left ventricular internal diastolic diameter, MAP – mean arterial pressure.

1.53, 95% CI: 1.16–2.01, P=0.002). The proportionality assumption was not violated (global test P = 0.90).

In the cohort of ALC ≤ 1500, 62.45% (336) patients died or were readmitted compared with 48.58% (239) in the cohort of ALC > 1500 (P < 0.001) (Table 1). By the PSM method, patients with ALC ≤ 1500 showed a higher hazard ratio for death or readmission at 30 days and 6 months (30-day HR 1.43, 95% CI:0.99–2.05, P=0.052; 6-month HR 1.55, 95% CI: 1.24–1.94, P < 0.001). The proportionality assumption was not violated (global test P = 0.60). Fig. 3 (Panel A-D) demonstrates Kaplan Meier graphs of all primary and secondary outcomes in propensity-score matched cohort. The log-rank test p-value for all the outcomes was statistically significant, as shown in the figures. Similar results were obtained using univariable and multivariable method for all secondary outcomes as shown in Supplemental Table 1.

1.2.4. Subgroup analysis by Ejection Fraction (Fig. 4)

We performed a sub-group analysis in HFREF and HFpEF to assess

primary and secondary outcomes using the PSM method. There were 466 patients in HFREF and 300 patients in HFpEF. We observed that ALC < 1500 cells/mm³ had a higher risk of mortality in both HFREF (HR 1.49, 95% CI: 1.06–2.10, P=0.022) and HFpEF (HR 1.49, 95% CI: 1.01–2.20, P=0.044) subgroups. In the subgroup of HFREF, patients with ALC < 1500 had a higher hazard of all-cause readmission at 30 days and 6 months. In the subgroup of HFpEF, patients with ALC < 1500 had a similar hazard of all-cause readmission at 30 days and 6 months. In the subgroup of HFREF, patients with ALC < 1500 had a higher hazard of cardiac readmission at 30 days and 6 months, but at 30 days, the estimate was statistically insignificant. In the subgroup of HFpEF, patients with ALC < 1500 had a similar cardiac readmission hazard at 30 days and 6 months. In the subgroup of HFREF, patients with ALC < 1500 had a higher hazard of a composite of death or readmission at 30 days and 6 months, but at 30 days, the estimate was statistically not significant. In the subgroup of HFpEF, patients with ALC < 1500 had a similar hazard of a composite of death or readmission at 30 days but had a higher hazard at 6 months.

Table 2

Baseline demographic and clinical characteristics of patients by absolute lymphocyte count after propensity-score matching.

	No Lymphopenia (ALC > 1500 cells/ mm ³) (N = 383)	Lymphopenia (ALC ≤ 1500 cells/mm ³) (N = 383)	P- value
Demographic			
Age (years), median (IQR)	64 (54 – 74)	63 (53 – 74)	0.67
Male, n (%)	154 (40.2)	150 (39.2)	0.768
Black, n (%)	157 (41)	164 (42.8)	0.608
Comorbidities			
Hypertension, n (%)	335 (87.5)	337 (88)	0.826
Diabetes, n (%)	198 (51.7)	210 (54.8)	0.385
CAD, n (%)	116 (30.3)	112 (29.2)	0.752
Stroke, n (%)	36 (9.4)	39 (10.2)	0.715
Cancer, n (%)	35 (9.1)	36 (9.4)	0.901
Atrial fibrillation, n (%)	88 (22.98)	88 (23)	1.00
Chronic lung disease, n (%)	73 (19.1)	70 (18.3)	0.781
Parameters on admission			
MAP (mm Hg), median (IQR)	102.67 (90.3 – 117.3)	100 (89.3 – 113.7)	0.17
BMI, median (IQR)	28.6 (24.9 – 35.3)	29.4 (25 – 35.7)	0.438
Pro-BNP (pg/ml), median (IQR)	5657 (1553–10317)	6567 (2217–12941)	0.33
Hb (g/dL), median (IQR)	12 (10.8 – 13.5)	12 (10.4 – 13.3)	0.18
GFR (ml/min/m ²), median (IQR)	62.5 (39.3 – 86.3)	61.2 (38.1 – 86.8)	0.66
Sodium (mEq/L), median (IQR)	139 (137–142)	139 (137 – 141)	0.48
Echocardiographic features			
EF > 40%, n (%)	146 (38.1)	154 (40.2)	0.554
LAD, median (IQR)	4.2 (4 – 4.8)	4.3 (4 – 4.9)	0.58
LVIDD, median (IQR)	5.5 (4.9 – 6)	5.5 (5 – 6.1)	0.80
Discharge medications			
Loop diuretics, n (%)	308 (80.4)	303 (79.1)	0.653
Beta blocker, n (%)	305 (79.6)	310 (80.9)	0.65
ACE inhibitors/ ARB, n (%)	290 (75.7)	289 (75.5)	0.933
CCB, n (%)	95 (24.8)	118 (30.8)	0.064
Spirolactone, n (%)	70 (18.3)	64 (16.7)	0.568
Digoxin, n (%)	101 (26.4)	102 (26.6)	0.935
Aspirin/ clopidogrel, n (%)	307 (80.2)	315 (82.3)	0.459
Anticoagulation, n (%)	66 (17.2)	63 (16.5)	0.772
Statin, n (%)	251 (65.5)	266 (69.5)	0.247
Outcomes			
Death, n (%)	112 (29.2)	130 (34.7)	0.104
All-cause readmission, n (%)	128 (33.4)	176 (46)	<0.001
Cardiac readmission, n (%)	93 (24.3)	129 (33.7)	0.004
Death or readmission, n (%)	192 (50.1)	238 (62.1)	0.001

Abbreviations ACE – angiotensin converting enzyme, ALC – absolute lymphocyte count, ARB – angiotensin receptor blocker, BMI – body mass index, CAD – coronary artery disease, EF – ejection fraction, GFR – glomerular filtration rate, Hb – hemoglobin, LAD – left atrial diameter, LVIDD – left ventricular internal diastolic diameter, MAP – mean arterial pressure.

The p-value for interaction between type of heart failure and lymphopenia was not significant for all the outcomes (Supplemental Table S2).

1.2.5. Degree of lymphopenia and mortality in full cohort and subgroups (Fig. 5. Panel A, B, C, Supplemental Table S3)

In the cohort of HF and subgroup of HF_rEF, we observed a graded relationship between the degree of lymphopenia and mortality risk. The lower group of ALC was associated with a higher risk of mortality. It was consistent and statistically significant in groups C and D. In the HF_pEF subgroup, we did not observe similar graded relationships likely due to insufficient power to detect the difference. We extrapolated the Kaplan-Meier graphs to demonstrate the association between ALC categories and mortality. We also showed linear association between ALC and all-cause mortality ($p = 0.035$).

1.3. Discussion

Significant findings of this study include the following: (1) ALC ≤ 1500 cells/mm³ is an independent predictor of mortality in heart failure and subgroups of HF_rEF and HF_pEF; (2) ALC ≤ 1500 cells/mm³ is an independent predictor of all-cause readmission, and a composite of death or readmission at 30 days and all-cause readmission, cardiac readmission, and composite of death or readmission at 6 months in heart failure; (3) in HF_rEF, ALC ≤ 1500 cells/mm³ is an independent predictor of all-cause readmission at 30 days and 6 months, cardiac readmission and composite of readmission or death at 6 months; (4) in HF_pEF, ALC ≤ 1500 cells/mm³ is an independent predictor of composite of readmission or death at 6 months; (5) four categories of ALC had a graded correlation with the risk of death in heart failure and subgroup of HF_rEF, but in HF_pEF it was not statistically significant, likely due to insufficient power.

One study has described the association between ALC and mortality at 1-year [16]. Few studies demonstrated other lymphocyte lineage methods such as NLR, PLR, or %L predicting mortality [5–10]. The study by Boralkar et al. [5] described NLR as an independent predictor of all-cause mortality in patients hospitalized with HF_pEF at 1, 2, or 3 years after admission. Huang et al. [17] showed that neutrophil count, NLR, reciprocal of lymphocyte, and PLR were independent predictors of mortality at 3 years. In a prospective longitudinal study, Charach et al. [18] found that ALC < 1600 cells/mm³ was an independent mortality predictor in patients with chronic HF_rEF in the ambulatory setting. Among these multiple hematological indices that include lymphocytes, reciprocal of lymphocyte appears to be the best predictor of mortality in a head-to-head comparison to white blood cell count, neutrophil count, NLR, and PLR [17]. However, ALC is not well-studied in hospitalized heart failure patients for long-term mortality and readmission; additionally, no literature has shown association between grading of ALC and mortality. We used ALC as a predictor and demonstrated similar mortality results in heart failure patients and its subgroups of HF_rEF and HF_pEF. Uthamalingam et al. [19] divided NLR into tertiles and showed higher tertile had the highest mortality and 30-day readmission hazard. We found similar results in groups C and D of ALC for mortality when ALC was divided into four categories in heart failure and the subgroup HF_rEF, which has not been described earlier. Minimal data are available on the association between ALC and other lymphopenia markers with readmission. One study [19] showed that a higher tertile of NLR is an independent predictor of 30-day readmission. In the current study, we assessed all-cause readmission, cardiac readmission, and a composite of readmission or death at short-term (30 days) and medium-term (60 days), which has not been studied prior for any lymphocyte marker.

The most accepted lymphopenia mechanism in heart failure is a state of chronic subclinical stress [20], inflammation [21] and sympathetic activation [22], where the cross-talk of this neuro-immuno-hormonal axis plays a critical role [23]. High cortisol levels [4,24], stimulation of beta-adrenergic receptor in the lymphocytes due to increased sympathetic tone [22], and elevated cytokines [25] have all shown to cause

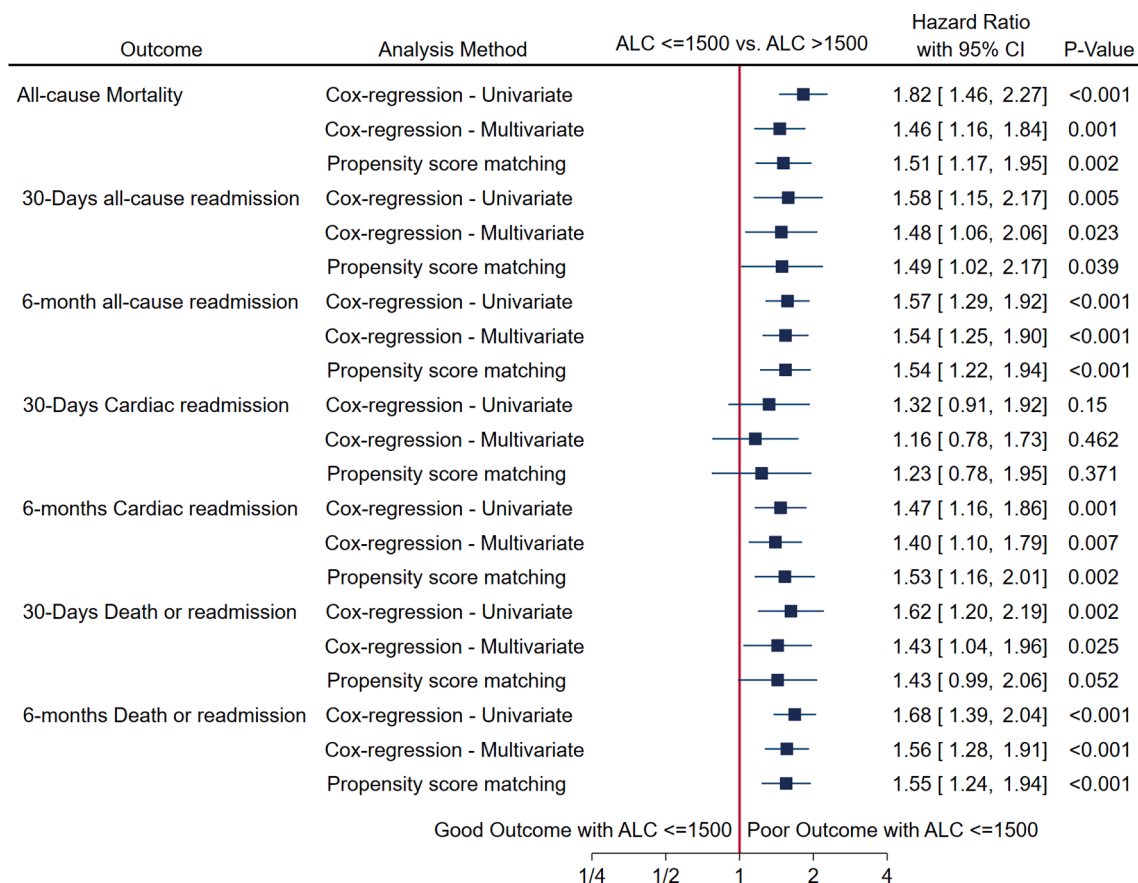


Fig. 2. Forest plot demonstrating primary and secondary outcomes in heart failure cohort by various methods.

lymphopenia. Systemic inflammation and the related cytokines in heart failure have been associated with the migration of monocytes to the myocardium, which leads to interstitial fibrosis and ventricular remodelling [26], leading to poor outcomes in HF. This further reflects our hypothesis that lymphopenia is associated with poor HF outcomes. It is important to stress that the cross-talk between immune, nervous and endocrinologic systems, and their effects on the heart is seen as a vicious cycle with no clear starting point [21]. Renin-angiotensin-aldosterone system inhibitors, mineralocorticoid antagonists, and beta-blockers prevent cardiac remodeling in HF that a chronic state of inflammation may partly drive. These therapies that have been proven to decrease mortality in patients with HF may affect the circulating lymphocytes [22]. It is tempting to speculate that ALC may serve as a measurement of response to a single or combination of these therapies [27,28]. This opens the avenue for future research to explore lymphopenia as a marker of response to HF treatment.

Treatments targeting cytokines in HF have been a focus of interest given that cytokine production by lymphocytes and monocytes have been previously demonstrated [29]. TNF- α is a known driver of lymphopenia via increased susceptibility to apoptosis [30]. Agnoletti et al. hypothesized that TNF- α production by monocytes in patients with advanced HF could be due to the mesenteric vascular congestion, resulting in bacterial translocation and endotoxin release, leading to a feedback loop of chronic inflammation²⁷. Targeting cytokines in HF, such as TNF- α [22,31], and IL-1 β [32,33], have failed to show mortality benefit in randomized clinical trials. Hence, we assume that the underlying chronic inflammatory status present in HF patients appears to be a consequence rather than a cause [21]. This could explain why targeting the immune system in HF patients may be further downstream of the cascade that causes HF progression.

1.4. Study limitations

Our study was single-center and retrospective in nature, and fraught with inherent unmeasured biases that might exist despite robust adjustments. However, the size of the study population, and the consistency of results with prior studies reassure that the conclusions may be more generalizable. We analyzed by multivariate cox-regression and propensity-score matching methods, utilizing 25 variables for the robust adjustment and matching. We used ALC as the single estimate point to predict mortality. We did not evaluate the changes of ALC through time (to assess their predictive power through time). Moreover, we used ALC over lymphocyte percentage as ALC is a direct estimate while lymphocyte percentage is an indirect estimate of lymphocyte. However, superiority of one over the other is not established. It is essential to note that we have excluded patients with conditions, as mentioned in exclusion criteria, that affect ALC level, which removes potential biases and gives us a focused cohort to evaluate ALC's role. Since inflammatory parameters such as CRP, procalcitonin, or ESR were not commonly obtained in routine laboratories in our patients' cohort, we could not correlate the severity of inflammation with the degree of lymphopenia. Though we obtained all the demographic, clinical, and laboratory characteristics from those hospitalized for the first time for HF in our medical center, we could not determine if prior admissions to other hospitals for HF exacerbation occurred. Also, patients might have had a readmission at a hospital outside our healthcare system, thereby not included in the study. However, given the large healthcare system and the specific patient population served by our hospital, it is very unlikely.

1.5. Conclusion

In conclusion, the present study showed that ALC could be a

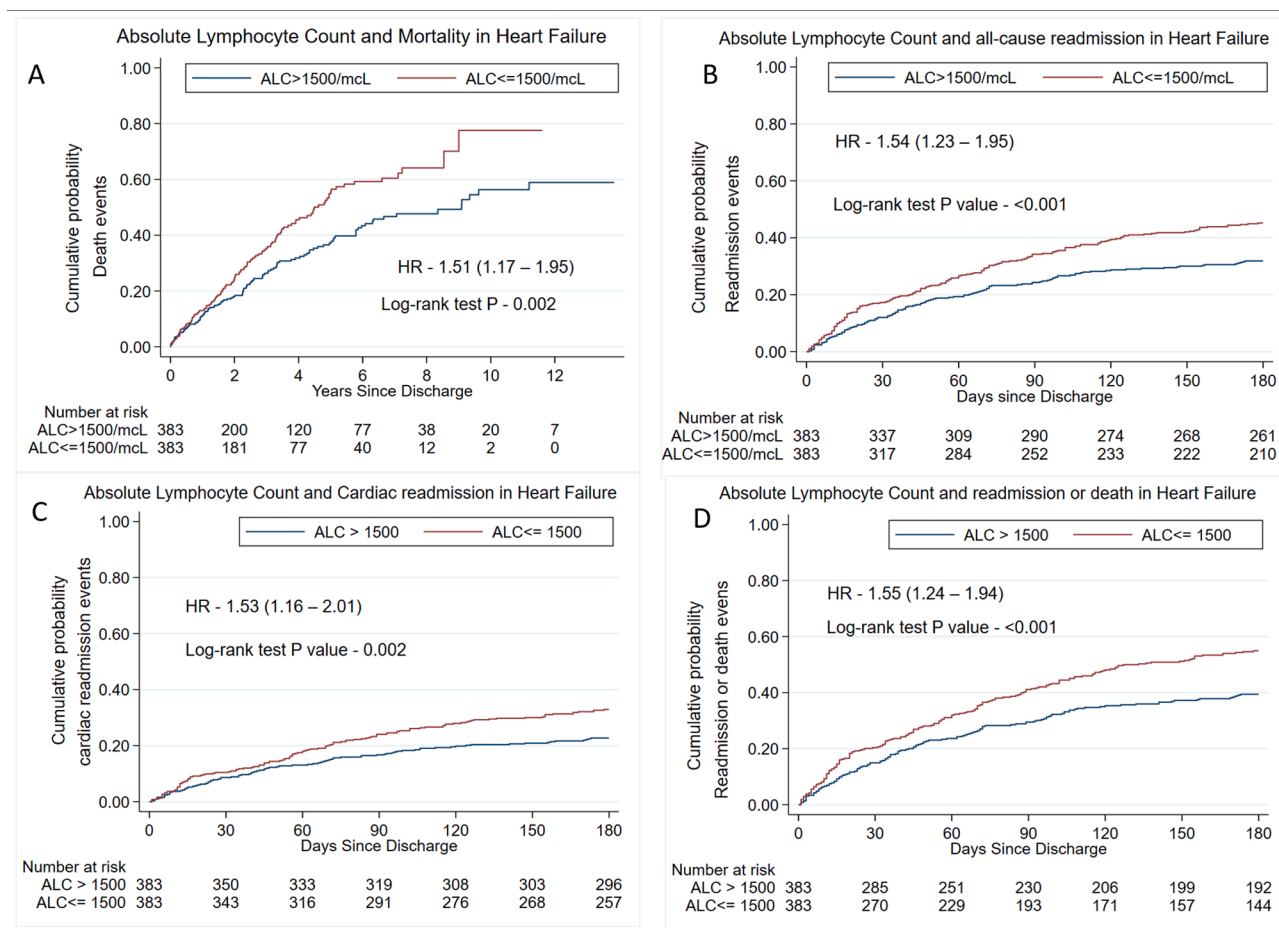


Fig. 3. Kaplan-Meier graphs for primary and secondary outcomes in propensity-score matched cohort, 3A. Kaplan-Meier graph of mortality; 3B. Kaplan-Meier graph of all-cause readmission, 3C. Kaplan-Meier graph of cardiac readmission; 3D. Kaplan-Meier graph of death or readmission.

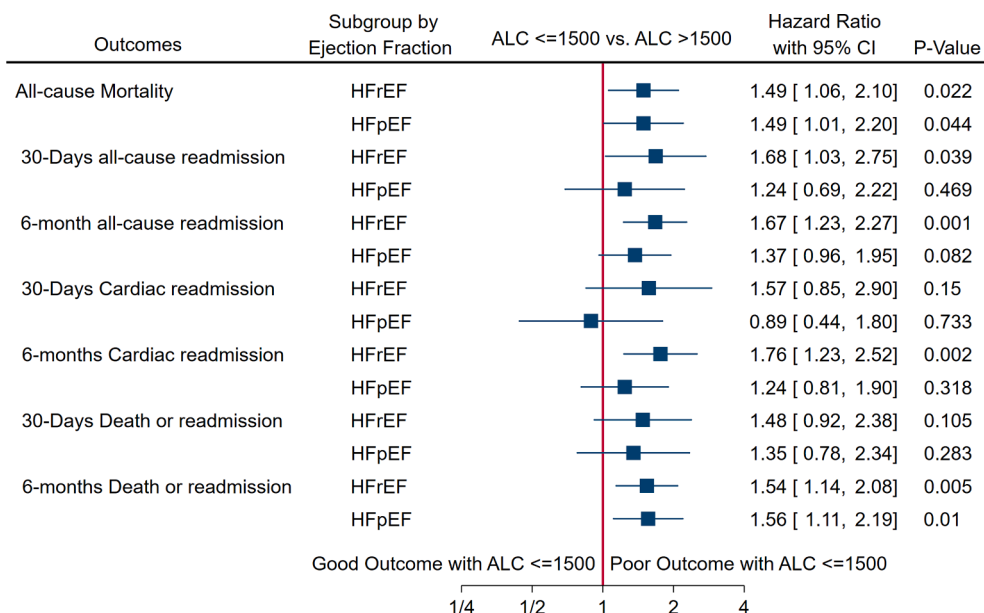


Fig. 4. Forest plot of primary and secondary outcomes in subgroups of HFrEF and HFpEF in PSM analysis.

predictor of mortality in heart failure patients and its subgroups of HFrEF and HFpEF. Categories of ALC showed graded correlation with mortality from a higher group (>2000 cells/mm³, 1501–2000 cells/

mm³ to lower group (≤1000 cells/mm³, and 1001–1500 cells/mm³). ALC is a good predictor of short-term (30-day) and medium-term (6-month) readmission-related outcomes in HF and HFrEF subgroups

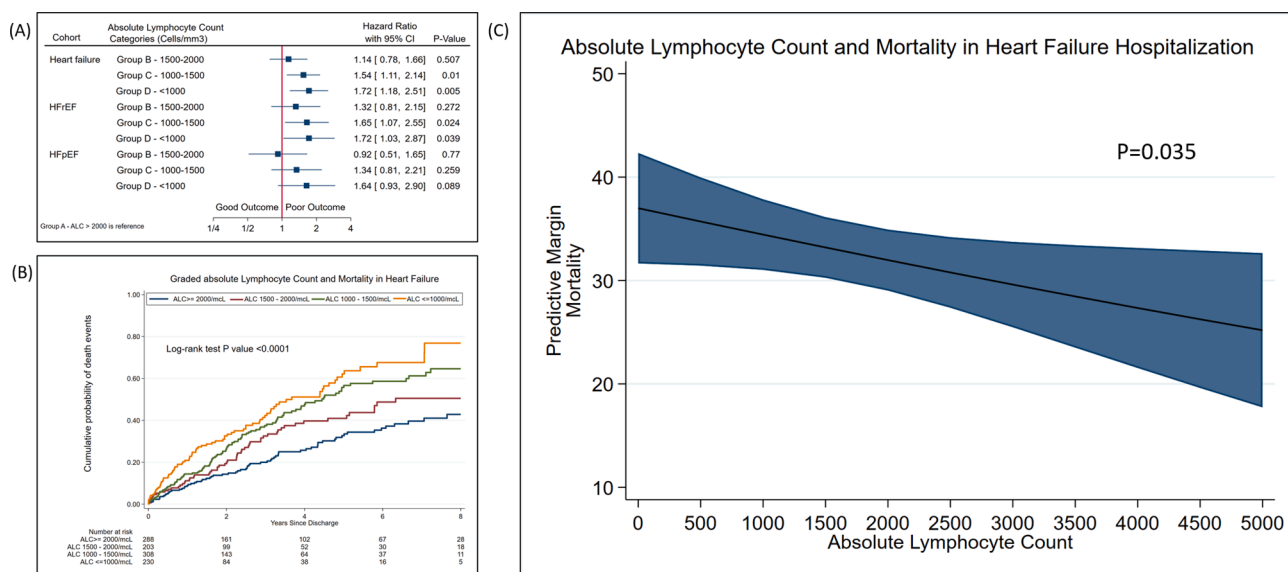


Fig. 5. Panel (A) Forest plot of mortality and ALC categories in PSM Model; Panel (B) Kaplan-Meier graph of mortality by lymphopenia categories; Panel (C) Spline graph showing ALC and all-cause mortality, lymphocyte \geq 2000 – reference group, lymphocyte 1500 – 2000 [HR (95% CI)] – 1.14 (0.78 – 1.65) P = 0.507, lymphocyte 1000 – 1500 – 1.54 (1.11 – 2.14) P = 0.010, lymphocyte \leq 1000 – 1.72 (1.18 – 2.52) P = 0.005.

except for short-term cardiac readmission. ALC is not a good predictor of readmission-related outcomes in patients with HFpEF, and remains to be further investigated with sufficient power. This study supports the incorporation of a cost-effective, readily available ALC in the prognostication model of heart failure due to its ability to predict outcomes in the short-term and medium-term duration.

Authorship Contribution

All authors participated in the research and preparation of the manuscript as per the International Committee of Medical Journal Editors (ICMJE).

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Dr. Kalra is CEO of makeadent.org. The authors reported no potential conflict of interest, relationships with pharmaceutical companies, biomedical device manufacturers, or other corporations whose products or services are related to the subject matter of the article.]

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2022.100981>.

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