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Research Article

Platelet-to-Lymphocyte Ratio (PLR) and Lymphocyte-to-Monocyte Ratio (LMR) at Admission Predict Survival in Hip Fracture Patients

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Abstract

Objectives: To investigate the value of PLR and LMR at admission for predicting in-hospital mortality in elderly patients with hip fracture (HF).

Design: Prospective study.

Setting: Academic, Level 1 trauma centre.

Intervention: None

Main Outcome Measurement: In-hospital mortality.

Patients: Main cohort: 1,256 consecutive HF patients (mean age 82.9 ± 8.7 years, 73.5% females), validation cohort: 582 HF patients (mean age 81.9 ± 9.13 years, 71.0% females).

Results: The in-hospital mortality rate was 5.0% (n=64) in the main cohort and 4.1% (n=24) in the validation cohort. Both elevated PLR (>280) and low LMR (<1.1) were significant independent prognostic indicators of hospital mortality. In aged >80 years with abnormal PLR or LMR, the risk of a fatal outcome was about 3-fold higher compared to the rest of the cohort and 10-15-fold higher compared to individuals without both characteristics. Admission PLR or LMR were highly predictive for a fatal outcome in patients aged >80 with comorbidities (CAD, CKD, COPD, dementia): area under the curve ranged between 0.827 and 0.873 and the number of patients needed to be examined for correct prediction ranged between 3.9 and 7.6. In the validation cohort, the admission PLR and LMR produced similar predictive values.

Conclusions: In HF patients, PLR and LMR at admission are independent prognostic indicators of in-hospital mortality and in combination with age >80 and certain comorbidities are strong predictors of survival.

Level of Evidence: Prognostic Level II. See Instructions for Authors for a complete description of levels of evidence.

Keywords: Elderly; Hip fracture; Mortality; Platelet-to-lymphocyte ratio (PLR); Lymphocyte-to-monocyte ratio (LMR)

Introduction

The number of hip fracture (HF) patients continue to rise worldwide due to population ageing. Early prediction of hospital outcomes in HF patients, one of the most challenging clinical conditions in the elderly, in whom multiple chronic comorbidities are common, is of great importance for stratifying the level of care and appropriate management. Accurate predicting HF outcomes on admission remains a long-term goal of orthogeriatrics. Currently clinicians do not have a single tool that can be easily administered and interpreted at admission. Previously we documented prognostic value of some preoperative laboratory variables combined with demographic and comorbid factors [1]. In this study we extended this approach focusing on two novel blood-based biomarkers - platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR), which are widely used as predictors of adverse outcomes in various (mostly oncological) diseases, especially in the elderly [2-4], but have not been fully evaluated for predicting in-hospital mortality in elderly HF patients. The aim of this study was to investigate the prognostic value of PLR and LMR at admission for predicting in-hospital mortality in elderly HF patients, especially aged >80 years with pre-fracture chronic diseases.

Methods

In a prospectively collected cohort of 1,256 consecutive patients (older than 65 years) admitted to the Department of Orthopaedics Surgery of our hospital with a HF (mean age 82.9 ± 8.7[SD] years, 50.5 % with cervical fracture, 73.5% females) we analyzed admission levels of PLR and LMR as well as the socio-demographic, clinical and numerous routine laboratory parameters in regard to in-hospital all-cause mortality. Detailed descriptions of this cohort, inclusion and exclusion criteria, have been published in another article [5]. Multivariate stepwise logistic regression analyses were performed with cut-offs for PLR >280 (the fourth quartile) and for LMR <1.1 (the first quartile). The receiver operating characteristic (ROC, area under the curve, AUC) was used to assess the predictive values of these ratios; the number of patients needed to be examined for correct prediction (NNP) was calculated [6]. All p values presented are two-tailed, p value <0.05 was considered significant. The analyses were performed using Stata software version 10 **(**StataCorp, College Station, TX, USA).

The validation cohort (n=582, mean age 81.9 ± 9.13 years, 52.9 % with cervical fracture, 71.0% females) had a similar to the main cohort profile of chronic comorbidities, admission laboratory characteristics and outcomes.

Ethical Approval

The study was performed in accordance with the Declaration of Helsinki (1964) and its later amendments (as revised in 2013). The study was approved by the Australian Capital Territory Human Research Ethics Committee (REGIS 2018/ETH00516). Informed consent was obtained from all patients or their carers.

Results

The in-hospital mortality rate was 5.0% (n=64). Most fatal outcomes occurred in patients aged>80 years (n =56, 87.5%), in whom the mortality rate was 6.2%, the highest mortality rate had patients with history of myocardial infarction (MI, 12.5%), followed by individuals with coronary artery disease (CAD, 9.4%), chronic kidney disease (CKD, 8.9%), chronic obstructive airway disease (COPD, 8.7%) or dementia (7.8%). Both elevated PLR and low LMR on admission were significant independent prognostic indicators of hospital mortality with OR of 2.10 and 2.07, respectively, after adjustment for 20 variables, each of which was significant on univariate analysis (Table 1). When PLR or LMR were assessed in aged >80 years, the risk of a fatal outcome was about 3-fold higher compared to the rest of the cohort and 10- 15-fold higher compared to individuals without both characteristics (i.e., age<80 years and no abnormal PLR or LMR). The prognostic values increased further significantly when presence of a chronic disease was included in the analyses.

Table 1: Prognostic value of admission platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) alone and in combination with advanced age and comorbidities in predicting hospital all-cause mortality in older patients with hip fracture.

		PLR > 280 (n=324, 25.8%)					LMR < 1.1(n=321, 25.6%)				
Model	A/B	OR [95%CI]	AUC [95%CI]	Sn, %	Sp, %	NNP	OR [95%CI]	AUC [95%CI]	Sn, %	Sp, %	NNP
Non-adjusted (n=1256)		2.29 [1.35, 3.89]	0.592 [0.527, 0.656]	43.4	75.0	23.3	2.31 [1.37, 3.90]	0.591 [0.528, 0.655]	42.6	75.7	22.6
*Adjusted (n=1256)		2.10 [1.21, 3.65]	0.726 [0.668, 0.785]				2.07 [1.20, 3.59]	0.742 [0.684, 0.800]			
¶Age>80 years (n=884, 70.4%)	A	2.96 [1.73, 5.06]	0.668 [0.610, 0.727]	40.0	81.6	15.9	2.70 [1.58, 4.62]	0.663 [0.535, 0.659]	37.7	81.7	17.6
	B	10.44 [3.10, 35.10]	0.752 [0.672, 0.832]	88.9	56.6	11.4	15.33 [3.58, 67.72]	0.772 [0.700, 0.845]	92.0	57.1	11.5
Age>80 years + CKD (n=359, 28.6%)	A	4.30 [2.30, 8.02]	0.708 [0.647, 0.768]	25.0	92.8	9.1	3.85 [2.04, 7.27]	0.705 [0.647, 0.764]	23.0	92.8	10.2
	B	39.59 [5.15, 304.31]	0.831 [0.765, 0.897]	93.8	72.5	6.9	39.10 [5.07, 301.78]	0.835 [0.765, 0.904]	93.3	73.6	7.4
Age>80 years + CAD (n=277, 22.1%)	A	6.66 [3.51, 12.66]	0.683 [0.618, 0.749]	25.0	95.2	5.9	6.05 [3.20, 11.43]	0.679 [0.615, 0.743]	24.6	94.9	6.4
	B	29.21 [6.49, 131.42]	0.839 [0.757, 0.921]	88.2	79.6	5.0	28.67 [6.39, 128.70]	0.838 [0.755, 0.920]	88.2	79.3	5.4
Age>80 years + MI (n=72, 5.7%)	A	6.31 [2.24, 17.70]	0.677 [0.617, 0.738]	8.3	98.6	5.5	7.64 [2.66, 21.96]	0.68 [0.621, 0.738]	8.2	98.8	4.6
	B	39.27 [7.09, 217.43]	0.827 [0.646, 1.000]	71.4	94.0	4.5	48.93 [8.71, 274.76]	0.833 [0.652, 1.000]	71.4	95.1	3.9
**Age>80 years + COPD (n=138, 11.0%)	A	3.01 [1.14, 8.00]	0.685 [0.626, 0.744]	8.3	97.1	12.5	4.24 [1.80, 9.95]	0.671 [0.612, 0.730]	11.5	97.0	8.4
	B	70.49 [3.82, 1302.57]		91.7	86.5	7.6	47.06 [5.62, 393.73]	0.873 [0.749, 0.997]	87.5	87.1	6.3
**Age>80 years + Dementia (n=347, 27.6%)	A	1.99 [0.96, 4.18]	0.692 [0.632, 0.752]	15.0	91.9	24.7	2.27 [1.08, 4.75]	0.69 [0.633, 0.747]	14.8	92.9	19.8
	B	11.74 [2.49, 55.3]	0.771 [0.649, 0.892]	81.8	72.3	13.0	53.79 [3.09, 937.59]		94.7	74.9	10.8

Abbreviations: OR, odds ratio; CI, confidence interval; AUC, area under the curve (receiver operating characteristic); Sn, sensitivity; Sp, specificity; NNP, number of patients needed to be examined for correct prediction; A, comparison with the rest of the cohort; B, comparison with patients without any of the three analysed characteristics. CKD, chronic kidney disease (estimated glomerular filtration rate <60 ml/min/1.73 m2, total n=411, 32.7%); CAD, coronary artery disease (n=366, 29.1%); MI, history of myocardial infarction (n=100, 8.0%); COPD, chronic obstructive airway disease (n=222, 17.7%); dementia (n=408, 32.5%).

*Adjusted for all clinical (n=9: Dementia, CKD, CAD, previous MI, COPD, transient ischaemic attack/stroke, anaemia, age and gender) and laboratory (n=11: red cell count, haemoglobin, haematocrit, red cell distribution, basophils, eosinophils, parathyroid hormone, urea, creatinine, albumin, ferritin) variables which were significantly associated with hospital mortality on univariate analyses ($p<0.05$). ¶This and all following models have been adjusted for gender. **There were no survivors among patient aged>80 years with COPD or dementia and PLR>280 or LMR<1.1, respectively. All presented results are statistically significant ($p<0.05$).

Patients aged >80 years with an abnormal haematologic marker on admission and one of four tested comorbidities (history of CAD, MI, CKD or COPD) have 3-7.6-fold higher risk of hospital death compared to the rest of the cohort. The risk was, understandably, much higher comparing to subjects without combination of three parameters: ORs ranged between 28.7 (for patients with CAD and LMR<1.1) and 70.1(for COPD patients and PLR >280). ROC demonstrated that in HF patients above 80 years of age an abnormal PLR or LMR at admission is highly predictive for a fatal outcome, especially in subjects with a history of CAD (AUC=0.839 and 0838, respectively), or CKD (AUC=0.831 and 0.835), or MI (AUC=0.827 and 0.833), or COPD (AUC=0.873 for LMR) compared to individuals without any of the three characteristics; the combined biomarkers showed also reasonable predictive values in comparison with rest of the cohort (AUC ranged between 0.605 and 0.730). Importantly, in most combined tests the sensitivity and specificity were quite high (87.1%-95.1%) and in all tests the negative predictive value (NPV) was above 99%. Moreover, combined three variables significantly decreased the number of patients needed to be examined/tested for a correct prediction (NNP): NNP among aged>80 years ranged between 3.9 (LMR<1.1 and history of MI) and 13 (PLR>280 and dementia) compared to 23 (when only a haematologic parameter was used) or 16-18 (when age> 80 years was also considered).

In the validation cohort (in-hospital mortality rate 4.1%), the admission PLR and LMR and the combined approach produced, in general, similar prognostic and predictive values. For example, risk of hospital death in aged >80 years with CAD and PLR>280 was 8.5 (95%CI 3.04-23.54) times higher than in the rest of the cohort (AUC =0.749, NNT 5.5) and 31.1-fold higher compared to patients without such signs (AUC=0.878, NNT 4.9); in case of LMR<1.1 the corresponding figures were: OR 4.3 (95%CI 1.36-13.52), AUC=0.713, NNT 10.1, and OR 18.31, AUC=0.810, NNT 8.0, respectively.

Discussion

Our findings indicate that in HF patients abnormal preoperative PLR and LMR, two simple, inexpensive and easily obtainable biomarkers, predict fatal outcome, especially in aged >80 years with a history of CAD, MI, CKD, COPD or dementia, and may help to identify the high-risk individuals who require more intensive therapy.

Currently the underlying mechanisms of the described associations remain poorly understood. Increased platelet and monocyte counts are known to be associated with inflammation, immune response and thrombosis, while lymphocytes have a major role in immune-surveillance and exert a protective effect. The observed association of worse/fatal prognosis with elevated PLR and low LMR, each of which combines actual information on these vital interrelated biological processes, is in line with the phenomenon of inflammageing and immunosenescence, the hallmarks of geriatric chronic diseases, including osteoporotic fractures [7-10]. The association between low-grade systemic inflammation (with an inadequate immune response) and osteoporosis, frailty, sarcopaenia, falls, fractures and survival has been widely demonstrated [11-15]. Apparently it would be worth investigating in longitudinal studies whether treatment aimed to normalise patient's immuno-inflammatory status (as it reflected in the studied ratios) changes the outcomes.

The limitations of this study include its observational design and single-center data; the deaths were not stratified according to causes (because the number of observations for each cause was small) and the study population consisted mainly of Caucasian patients indicating a need for larger, preferably multicenter prospective, studies.

Conclusions

In HF patients, abnormal PLR (>280) and LMR (<1.1) at admission are independent prognostic indicators of in-hospital mortality and in combination with advanced age (>80 years) and chronic comorbidities are strong predictors of survival.

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