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Lower mean platelet volume is a risk indicator of hepatocellular carcinoma recurrence following liver transplantation

Ai-Bin Zhang[a], Zhi-Hao Zhang[b], Jie Zhang[c], Bing-Yi Lin[a,b], Lei Geng[a,b], Zhe Yang[a,b], Xiao-Ning Feng[a], Shu-Sen Zheng[a,b,*]

[a] *Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China*
[b] *Key Laboratory of Combined Multi-Organ Transplantation, Ministry of Public Health, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China*
[c] *Department of Hepatobiliary Surgery, The First Hospital of Jiaxing, Jiaxing University, Jiaxing 314000, China*

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ABSTRACT

Background: Lower mean platelet volume (MPV) is an indicator of platelet activity in the setting of tumor development. This study was to assess the relationship between preoperative MPV and survival outcomes of patients with hepatocellular carcinoma (HCC) following liver transplantation (LT).

Methods: The demographic and clinical characteristics of 304 HCC patients following LT were retrieved from an LT database. All the patients were divided into the normal and lower MPV groups according to the median MPV. The factors were first analyzed using a Kaplan–Meier survival analysis, then the factors with $P < 0.10$ were selected for multivariate Cox regression analysis and were used to define the independent risk factors for poor prognosis.

Results: The 1-, 3-, and 5-year tumor free survival was 95.34%, 74.67% and 69.29% in the normal MPV group, respectively, and 95.40%, 59.97% and 42.94% in the lower MPV group, respectively ($P < 0.01$). No significant difference was observed in post-LT complications between the normal and lower MPV groups. Portal vein tumor thrombosis (PVTT) [hazard ratio (HR = 2.24; 95% confidence interval: 1.46–3.43; $P < 0.01$) and lower MPV (HR = 1.58; 95% confidence interval: 1.05–2.36; $P = 0.03$) were identified as independent prognostic risk factors for recipient survival.

Conclusion: Preoperative lower MPV is a risk indicator of HCC patients survival outcomes after LT.

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Introduction

Hepatocellular carcinoma (HCC) is one of the major causes of cancer-related death worldwide [1]. The HCC incidence rate is higher in China than other countries, and new Chinese HCC patients annually account for over half of the cases worldwide, largely due to the high prevalence of hepatitis B virus infection. Moreover, the aging of the population is another factor of HCC increase for society [2]. Liver transplantation (LT) is the most effective curative therapy for HCC patients [3]. However, the utility of LT is significantly restricted by the shortage of donor livers [4]. Furthermore, despite great advances in perioperative management, the rate of HCC recurrence and metastasis remains high after LT, even with administration of several new agents such as sorafenib and PD-1 antibody [4,5]. According to previous study, HCC patients within Milan criteria of LT still presented about 25% of tumor recurrence following LT [6]. To further decrease the tumor recurrence rate and effectively utilize donor livers, a precise biomarker that predicts tumor recurrence after LT and further optimize LT criteria are urgent.

In recent years, many noninvasive indicators from blood such as C-reactive protein (CRP) [7], neutrophil-lymphocyte ratio (NLR) [8], absolute monocyte count (AMC) [9], lymphocyte-monocyte ratio (LMR) [10], mean platelet volume (MPV) [11], and platelet-to-lymphocyte ratio (PLR) [12] have been demonstrated as convenient parameters for immune response in many diseases, including malignancy. Considering the close relationship between tumor development and the disturbance of immune function, an increasing number of studies have concentrated on exploring the value of aforementioned circulating indicators in predicting tumor recurrence and survival outcomes. Tadmor et al. [13] confirmed

* Corresponding author at: Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China.
E-mail address: shusenzheng@zju.edu.cn (S.-S. Zheng).

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that patients with nodular sclerosis Hodgkin's lymphoma with an AMC > 750 cells/mm^3 or LMR > 2.1 had shorter progression-free survival (PFS) at 10 years; both AMC and LMR maintained prognostic significance for PFS in multivariate Cox regression analysis. Among hematologic parameters, NLR was first investigated in predicting tumor recurrence after LT. Motomura et al. [14] revealed that HCC patients with high NLR presented higher serum and peritumoral IL-17 levels compared with the normal NLR group and had a lower 5-year tumor free survival (TFS) rate after LT. Kalra et al. [15] verified that high NLR was associated with proinflammatory neutrophils, and precisely predicted prognosis in patients with low scores of the Model for End-Stage Liver Disease (MELD) following LT. In addition, CRP and AMC also play important roles in predicting HCC recurrence after LT [9,16]. However, few studies have investigated the correlation between platelet related parameters such as platelet amount and MPV and prognosis of HCC patients with LT.

Elevated platelet counts and excessive blood coagulation in cancer patients were revealed in 1865. After that, many studies verified that platelet activation induces epithelial-mesenchymal transition (EMT), promotes tumor metastasis [17], protects cancer cells from shear stress [18], and increase the ability of cell adhesion, migration and proliferation [19]. MPV is a marker of platelet size and activity and is routinely reported during complete blood count analysis. Emerging evidence supports the use of MPV as an accessible biomarker predicting survival outcomes in malignant patients [20]. The present study aimed to investigate the role of MPV levels in HCC patients following LT, to evaluate whether it is a potential predictor of patient survival.

Methods

Patients

The data from histopathologically confirmed HCC patients undergoing LT from the First Affiliated Hospital, Zhejiang University School of Medicine between January 2010 and December 2017 were retrospectively reviewed. The livers were from the patients of cardiac death. Patients with ABO incompatible LT, steroids administration, autoimmune liver diseases, alcohol abuse and loss to follow-up were excluded from this study. The platelet and MPV levels were measured at the final routine blood test before LT. All the patients were divided into the normal and lower MPV groups according to the median MPV of 11.30 fl (range, 7.40–14.30 fl). Informed consent was received from all patients before conducting LT. This study obtained the approval from the Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine.

Management for patients following liver transplantation

After LT, patients were monitored in an intensive care unit (ICU). A standard immunosuppression strategy including methylprednisolone, tacrolimus, and mycophenolate mofetil (MMF) was administered to prevent rejection of graft. Among them, a fixed dosage of 0.5 g MMF was administered twice daily, methylprednisolone was administered initially at 1000 mg, then tapered and withdrawn in one month. For tacrolimus administration, the initial plasma target level was 10–12 ng/mL for the first month, and then titrated down and maintained at 5–10 ng/mL later. Lamivudine and hepatitis B immunoglobulin were administered against hepatitis B recurrence. The graft function was monitored with biochemical tests, emission computed tomography and ultrasonography. Liver biopsy was performed when considering rejection.

Statistical analysis

The data were shown as means with standard deviation (SD) and frequency. The independent sample *t*-test, Fisher's exact test and Pearson's χ^2 test were utilized to determine the differences of clinicopathologic factors between the lower and normal MPV groups. The risk factors for HCC recurrence were first defined with the Kaplan–Meier method, and factors with $P \leq 0.10$ were further analyzed with multivariate Cox regression analysis to estimate their hazard ratio. All analyses were performed using SPSS software version 20.0 (IBM, Armonk, NY, USA), and a $P < 0.05$ was considered statistically significant.

Results

Patients demographics and tumor information

A total of 304 liver recipients were enrolled in the study. Briefly, 220 (72.4%) patients were men and 84 (27.6%) were women. The median age was 53 years (range: 31–69 years) at time of transplantation. The median preoperative MPV, international normalized ratio, albumin, CRP, total bilirubin, and serum creatinine (Scr) were 11.30 fl, 1.16, 37.49 g/L, 16 mg/L, 43.88 μmol/L, 70.50 μmol/L, respectively. The effects of these factors on TFS were analyzed with Kaplan–Meier method according to their median values. A total of 84 patients had portal vein tumor thrombus (PVTT), 124 had more than 3 tumors and 87 showed largest tumor diameter above 5 cm. Recipients were divided into two groups according to the median MPV. Differences in demographic information and tumor characteristics between the two groups were presented in Table 1. Patients with lower MPV had significantly higher CRP, higher PVTT rate, more tumor number (>3), and larger tumor size.

Survival outcomes of recipients

The median follow-up time was 39.7 months (range: 5.8–106 months). The 1-, 3- and 5-year TFS rates were 95.38%, 65.49% and 53.79%, respectively. Death was verified for 116 patients, and 4 recipients received a second LT during follow-up. Post-LT tumor recurrence was the leading cause of death (104 patients). Other causes of deaths included sepsis/multiorgan dysfunction (4 patients), bleeding (2 patients), recurrent hepatitis B (2 patients), cardiovascular complication (2 patients). The cause of the 2 recipients' death remains unclear.

Relationship between MPV and TFS, complications

To investigate whether MPV was a marker for predicting survival outcomes of patients after LT, a univariate analysis was first conducted. The results confirmed that Scr > 70.50 μmol/L, AFP > 400 μg/L, PVTT, tumor number > 3, and lower MPV were risk factors of poor TFS ($P \leq 0.10$). These factors were selected to enter into multivariate Cox regression analysis, where PVTT (HR = 2.24; 95% confidence interval: 1.46–3.43; $P < 0.01$) and lower MPV (HR = 1.58; 95% confidence interval: 1.05–2.36; $P = 0.03$) were confirmed as independent risk factors (Table 2). The respective 1-, 3-, and 5-year TFS rates were 95.34%, 74.67% and 69.29% in the normal MPV group and 95.40%, 59.97% and 42.94% in the lower MPV group ($P<0.01$, Fig. 1A). Furthermore, no matter in patients within or beyond Milan criteria, the lower MPV maintains the predictive value for worse TFS (Fig. 1B and C).

The main complications following LT included infectious diseases, diabetes, biliary complications, bleeding, acute rejection, renal dysfunction, hypertension and metabolic complications. A total of 32 recipients suffered acute rejection following LT, which

Table 1
The demographic information and tumor characteristics in the two groups.

Variables	Lower MPV ($n = 149$)	Normal MPV ($n = 155$)	P value
Age (yr, mean ± SD)	51.34 ± 8.91	53.06 ± 7.93	0.076
Sex			0.200
Male	113 (75.8%)	107 (69.0%)	
Female	36 (24.2%)	48 (31.0%)	
Preoperative albumin (g/L)	37.40 ± 5.62	37.58 ± 4.89	0.770
Preoperative AFP > 400 μg/L	40 (26.8%)	34 (21.9%)	0.350
Preoperative CRP (mg/L)	41.41 ± 52.64	26.80 ± 32.39	**0.004**
Preoperative total bilirubin (μmol/L)	41.17 ± 68.30	46.48 ± 74.00	0.510
Preoperative Scr (μmol/L)	72.50 ± 24.40	70.90 ± 20.08	0.530
Preoperative INR	1.17 ± 0.19	1.21 ± 0.22	0.090
Child-Pugh score	10.21 ± 1.43	9.87 ± 1.72	0.060
Diabetes	14 (9.4%)	18 (11.6%)	0.580
Hypertension	27 (18.1%)	19 (12.3%)	0.200
HE	2 (1.3%)	3 (1.9%)	ns
FK506 (ng/mL) *	4.47 ± 2.23	4.71 ± 2.54	0.380
Total ischemia time (min)	274.35 ± 192.54	251.26±224.68	0.340
PVTT	50 (33.6%)	34 (21.9%)	**0.030**
Tumor number > 3	70 (47.0%)	54 (34.8%)	**0.036**
The largest tumor diameter > 5 cm	51 (34.2%)	36 (23.2%)	**0.042**
Differentiation			0.052
Well	63 (42.3%)	83 (53.5%)	
poor	86 (57.7%)	72 (46.5%)	

* Concentration of FK506 at post-operative 1 month. AFP: Alpha fetoprotein; Scr: serum creatinine; INR: international normalized ratio; HE: hepatic encephalopathy; PVTT: portal vein tumor thrombus; ns: no sense.

Table 2
Univariate and Multivariate analysis of variables influencing TFS after LT.

Variables	Univariate analysis		Multivariate analysis	
	P value	HR (95% CI)	P value	HR (95% CI)
Sex (male)	0.82	1.05 (0.68–1.63)		
Age (>53 yr)	0.24	0.79 (0.53–1.17)		
Preoperative albumin (>37.49 g/L)	0.31	0.82 (0.56–1.20)		
Preoperative CRP (>16 mg/L)	0.29	1.35 (0.77–2.36)		
Preoperative total bilirubin (>43.88 μmol/L)	0.76	1.06 (0.72–1.57)		
Preoperative INR (>1.16)	0.89	1.03 (0.69–1.52)		
Preoperative Scr (>70.50 μmol/L)	**0.10**	1.39 (0.94–2.01)	0.34	0.99 (0.98–1.01)
Hypertension	0.59	0.84 (0.45–1.58)		
Diabetes	0.14	0.54 (0.24–1.23)		
AFP > 400 μg/L	**0.01**	1.74 (1.14–2.67)	0.13	1.40 (0.90–2.17)
PVTT	**<0.01**	1.97 (1.29–3.01)	**<0.01**	2.24 (1.46–3.43)
Tumor number > 3	**0.03**	1.53 (1.03–2.23)	0.52	0.87 (0.57–1.31)
The largest tumor diameter > 5 cm	0.12	1.38 (0.93–2.01)		
Differentiation	0.14	1.38 (0.90–2.10)		
Lower MPV	**0.04**	1.51 (1.02–2.23)	**0.03**	1.58 (1.05–2.36)

HR: hazard ratio; 95% CI: 95% confidence internval; CRP: C-reactive protein; INR; international normalized ratio; Scr: serum creatinine; AFP: alpha fetoprotein; PVTT: portal vein tumor thrombus; MPV: mean platelet volume.

Table 3
Incidence of postoperative complications in patients with lower or normal MPV.

Variables	Lower MPV ($n = 149$)	Normal MPV ($n = 155$)	P value
Virus infection	8 (5.4%)	8 (5.2%)	0.86
Bacterial infection	6 (4.0%)	8 (5.2%)	0.84
Fungal infection	2 (1.3%)	4 (2.7%)	0.72
Mixed infection	4 (2.7%)	2 (1.3%)	0.62
Diabetes	2 (1.3%)	2 (1.3%)	0.64
Biliary complications	19 (12.8%)	14 (9.0%)	0.39
Bleeding	10 (6.7%)	14 (9.0%)	0.59
Acute rejection	14 (9.4%)	18 (11.6%)	0.66
Renal dysfunction	7 (4.7%)	13 (8.4%)	0.29
Hypertension	9 (6.0%)	8 (5.2%)	0.93
Metabolic complications	20 (13.4%)	19 (12.3%)	0.89

was verified by liver biopsy according to the Banff criteria. Subsequent augmentative steroid administration was effective. Finally, there were no differences in complications between the lower MPV group and the normal MPV group (Table 3).

Discussion

HCC is a highly malignant cancer that is common worldwide, and it presents high rates of tumor recurrence following LT, even in patients within Milan criteria [21]. Therefore, identifying a precise predictor for HCC recurrence to modify LT criteria is necessary for effectively utilizing donor livers. The main finding of this study is that lower MPV significantly correlated with poor tumor characteristics and poor prognosis of HCC patients after LT. Moreover, multivariate Cox regression analysis verified that PVTT and lower MPV were the independent risk factors for HCC recurrence. It is well known that platelets are an essential promotor for tumor cell proliferation and metastasis [22]. The α-granules and microvesicles from activated platelets contain plenty of growth factors, such as epidermal growth factor (EGF) [23], transforming growth factor (TGF-β) [24], platelet-derived growth factor (PDGF) [25] and hepatocyte growth factor (HGF) [3]. These factors promote tumorigenesis, tumor growth, tumor cell extravasation, and metastasis. Among them, TGF-β also decreases expression levels of natural

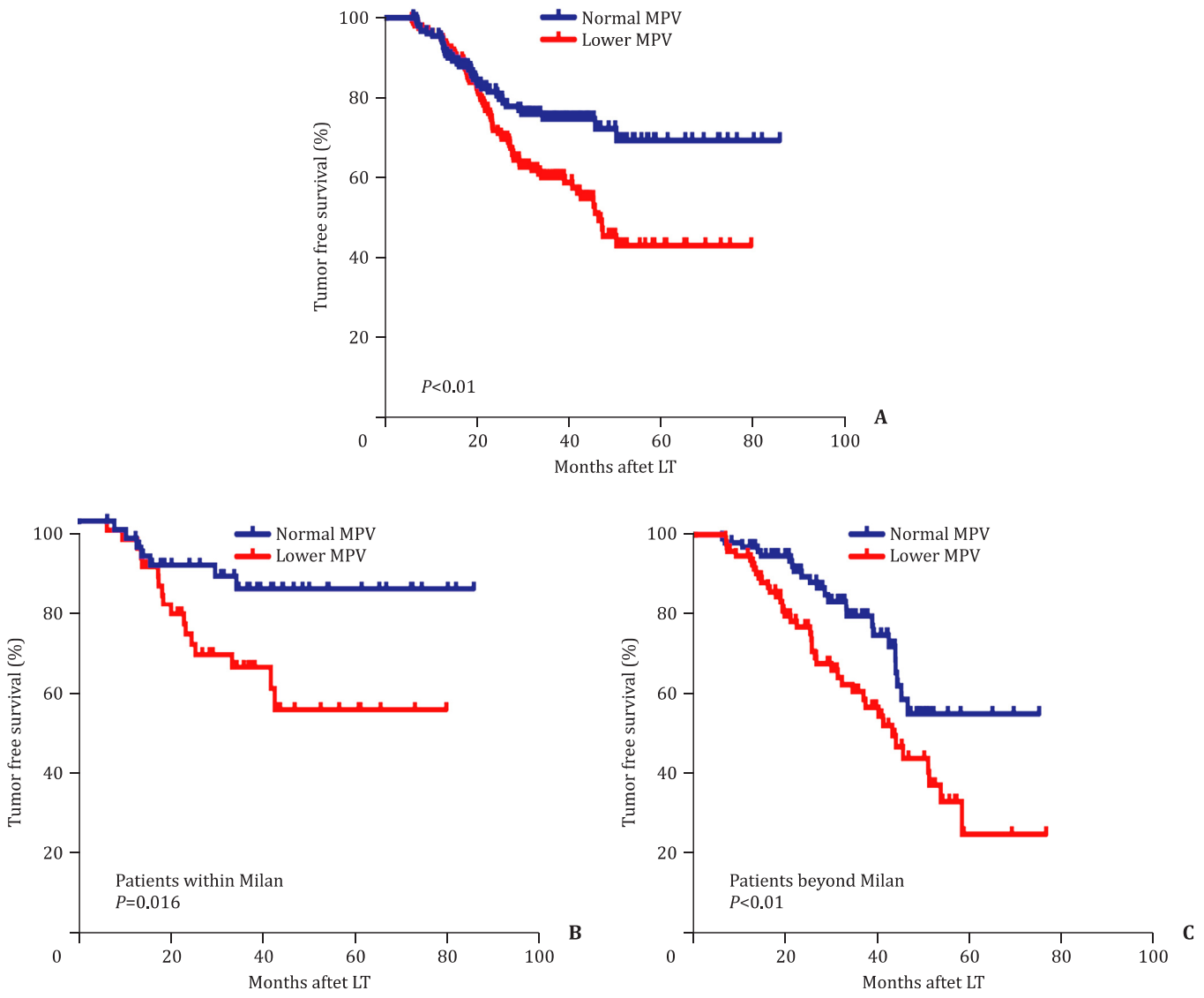

Fig. 1. Kaplan-Meier results for TFS for patients classified according to their preoperative MPV (**A**). In addition, recipients were further divided into within Milan criteria (**B**) group and beyond Milan criteria group (**C**), and the lower MPV maintained the predictive value. TFS: tumor free survival; MPV: mean platelet volume.

killer group 2D (NKG2D) on NK cells to inhibit NK cell activity and protect tumor cells from immune surveillance [26]. In addition, platelets could directly contact with tumor cells and activate the NF-κB signaling pathway to stimulate epithelial to mesenchymal transition [17]. Simon and coworkers demonstrated that long-term use of aspirin inhibits platelet activation and prevents hepatocarcinogenesis [27]. These data and our results suggest that activated platelet ratio is potentially associated with tumor recurrence. However, most of the methods for measuring parameters reflecting platelet activation are expensive, unstable and not commonly performed in clinical practice. We introduced MPV as an available indicator of platelet activation. MPV is included in routine blood examination and therefore, easy to obtain before LT.

Emerging evidences support the feasibility of MPV as a promising predictor of prognosis in patients with various diseases. Choi et al. [28] demonstrated that an upregulated MPV was a risk factor for ischemic stroke in patients with atrial fibrillation (AF); upregulation of MPV correlated with poor prognosis for patients with coronary artery disease following percutaneous coronary intervention (PCI). Avci et al. [29] also revealed that a high ΔMPV was observed in nonsurvivors compared to survivors with ST segment elevation myocardial infarction (STEMI) after primary PCI and acted as an independent predictor of mortality. Shen et al. [20] recommended the cut-off value for MPV to be 7.4 fl in esophageal cancer patients, and patients with lower MPV showed significantly worse survival outcomes compared to those with normal MPV. Furthermore, Chang et al. [30] confirmed that lower MPV may act as a predictive factor for survival in metastatic colorectal cancer patients treated with first-line chemotherapy. These studies suggested that either high or lower MPV is involved in the diseases progression and correlated with poor prognosis. This seems contradictory but, according to a previous report, both high and lower MPV indicated the presence of increased platelet activation.

The mechanism underlying the change of MPV remains unclear. Platelets with bigger size are usually observed when generated from bone morrow megakaryocytes [31]. Platelets from the human spleen presented approximately 20% larger MPV than platelets in circulating blood [32]. Moreover, large platelets are functionally hyperactivated and contain a high granule content consisting of procoagulant surface proteins and intracellular thromboxane A2 [33]. Hence, high MVP is a marker of a prothrombotic state, and appears in circumstances of fast changes in number of circulating platelets

such as thrombogenesis [34]. Lower MPV is commonly presented in related high grade inflammatory diseases such as active rheumatoid arthritis, advanced tumors and Takayasu arteritis [35], and it is considered an indicator for consumption of the platelet granule.

The main limitations of the present study are: a relatively small sample size from a single transplant center; factors, such as smoking, hypertension, dyslipidemia, diabetes and life style, which may influence MPV, were not analyzed. Therefore, the application of MPV in clinical practice still needs further investigation.

In conclusion, lower MPV correlated with poor tumor characteristics and high rate of tumor recurrence in HCC patients after LT, which may serve as a promising biomarker for selecting LT candidates.

Contributors

ZAB and ZSS conceived and designed the study; LBY and GL collected the data; ZZH, YZ, and FXN analyzed and interpreted the data; ZAB and ZJ drafted the manuscript. All authors contributed to the analysis and preparation of the manuscript. ZSS is the guarantor.

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Ethical approval

This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine (2018–0072).

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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