Correlation between Mean Platelet Volume and Vascular Access Events in Maintenance Hemodialysis Patients: Postprint

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Abstract

Background Arteriovenous fistula is the primary vascular access for maintenance hemodialysis (MHD) patients. Mean platelet volume (MPV) is a biomarker for cardiovascular events and has been identified as an independent risk factor for myocardial infarction, stroke, and venous thromboembolism. Whether MPV constitutes a risk factor for vascular access events in MHD patients remains unclear.

Objective To investigate the association between MPV levels and the risk of vascular access events in MHD patients.

Methods A total of 343 MHD patients treated at the Blood Purification Center of the Fourth Hospital of Hebei Medical University between September 1–15, 2020 were enrolled. Follow-up concluded on September 15, 2021. Endpoint events were defined as vascular access events (arteriovenous fistula stenosis or thrombosis) or patient death. Patients were stratified into four groups based on MPV quartiles: Q1 (MPV: 6.1–8.1 fL), Q2 (MPV: 8.2–8.8 fL), Q3 (MPV: 8.9–9.6 fL), and Q4 (MPV: 9.7–14.1 fL). General characteristics, laboratory parameters, and incidence of arteriovenous fistula thrombosis and stenosis were compared among groups. Kaplan-Meier survival analysis was performed to assess vascular access event incidence, with intergroup comparisons conducted using the Log-rank test. Multiple Cox proportional hazards regression models were employed to analyze the relationship between MPV and vascular access event risk, with additional subgroup analyses based on stratification characteristics.

Results Among 343 MHD patients, 60 (17.5%) developed vascular access events. The incidence rates in Q4, Q3, Q2, and Q1 groups were 33.7%, 17.8%, 12.2%, and 5.9%, respectively. Kaplan-Meier survival analysis revealed statistically significant differences in vascular access event incidence among the four

groups (^{2}=25.691, P<0.05). After adjusting for confounding factors, elevated MPV remained an independent risk factor for vascular access events (HR=1.59, 95%CI=1.28–1.97, P<0.001), with increasing risk corresponding to higher MPV levels (P for trend <0.001). Subgroup analyses demonstrated a significant interaction in the diabetes stratification (P for interaction <0.05), but not in other subgroups.

Conclusion Elevated MPV may represent a risk factor for vascular access events in MHD patients, providing a valuable reference index for clinicians to predict the risk of such events.

Full Text

Correlation between Mean Platelet Volume and Vascular Access Events in Maintenance Hemodialysis Patients

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Abstract

Background Arteriovenous fistula is the primary vascular access for patients on maintenance hemodialysis. Mean platelet volume (MPV) is a biomarker for cardiovascular events and has been identified as an independent risk factor for myocardial infarction, stroke, and venous thromboembolism. Whether MPV is a risk factor for vascular access events in patients with maintenance hemodialysis (MHD) is unclear.

Objective To explore the correlation between MPV levels and the risk of vascular access events in MHD patients.

Methods A total of 343 patients undergoing MHD at the Blood Purification Center of the Fourth Hospital of Hebei Medical University from September 1st to 15th, 2020 were selected for the study. The follow-up cutoff was September 15, 2021, and the endpoint events were the occurrence of a vascular access event (stenosis or thrombosis of the arteriovenous fistula) or patient death. Patients were categorized into 4 groups according to the quartiles of MPV values: Q1 group (MPV: 6.1–8.1 fL), Q2 group (MPV: 8.2–8.8 fL), Q3 group (MPV: 8.9–9.6 fL), and Q4 group (MPV: 9.7–14.1 fL). General conditions, laboratory tests, and incidence rates of arteriovenous fistula thrombosis and stenosis were compared among the four groups. Kaplan-Meier survival curves were used to analyze the incidence of vascular access events in MHD patients, with Log-rank test used for intergroup comparisons. The correlation between MPV and the risk of vascular access events in MHD patients was analyzed using multiple Cox proportional

hazard regression models, with further subgroup analyses performed based on stratified characteristics.

Results Vascular access events occurred in 60 (17.5%) of the 343 MHD patients. The incidence rates of vascular access events in the Q4, Q3, Q2, and Q1 groups were 33.7%, 17.8%, 12.2%, and 5.9%, respectively. Kaplan-Meier survival curve analysis showed a statistically significant difference in vascular access event incidence among the four groups ($^2 = 25.691$, $P < 0.05$). After adjusting for confounding factors, elevated MPV levels remained a risk factor for vascular access events in MHD patients (HR = 1.59, 95%CI = 1.28–1.97, $P < 0.001$), with the risk increasing as MPV levels rose (P for trend < 0.001). Subgroup analysis showed no interaction between subgroups except for the diabetes stratification (P for interaction < 0.05).

Conclusion Elevated MPV levels may be a risk factor for vascular access events in MHD patients, providing a reference index for clinicians to predict the risk of such events.

Keywords Hemodialysis; Maintenance hemodialysis; Mean platelet volume; Vascular access events; Arteriovenous fistula

Introduction

Arteriovenous fistula is the preferred vascular access for maintenance hemodialysis (MHD) patients. However, adverse vascular access events such as arteriovenous fistula thrombosis and stenosis have substantially impacted global healthcare resources [1-2]. Recent studies have found that mean platelet volume (MPV), as an important marker of platelet function, is closely associated with enhanced platelet reactivity [3] and increased in vitro aggregation [4] when abnormally elevated. MPV has been established as an independent risk factor for cardiovascular and cerebrovascular diseases and venous thromboembolism [5-8]. Therefore, this study aims to investigate the role and value of MPV in vascular access events among MHD patients, providing new clues for preventing such events.

Methods

1.1 Study Subjects

Patients undergoing MHD treatment at the Blood Purification Center of the Fourth Hospital of Hebei Medical University from September 1–15, 2020 were enrolled. Inclusion criteria were: (1) age $\geq$ 18 years; (2) using autogenous arteriovenous fistula (AVF) or arteriovenous graft (AVG) as vascular access; (3) receiving hemodialysis for more than 3 months, with frequency of 2–3 sessions per week, 4 hours per session. Exclusion criteria were: (1) missing laboratory data; (2) platelet count $< 50 \times 10^9$/ L; (3) psychiatric illness or critical condition

preventing cooperation; (4) refusal to participate or inability to provide informed consent. This study was approved by the Medical Ethics Committee of the Fourth Hospital of Hebei Medical University (approval No. 2020ky189).

1.2 Data Collection

Basic characteristics and general data were collected, including age, sex, BMI, dialysis vintage, weekly dialysis time, urea clearance index (Kt/V), systolic blood pressure, diastolic blood pressure, comorbidities, smoking history, and medication history. Pre-dialysis fasting venous blood samples were obtained to measure platelet count, MPV, C-reactive protein (CRP), serum albumin, serum calcium, serum phosphorus, β_2-microglobulin, serum potassium, carbon dioxide, and intact parathyroid hormone (iPTH).

1.3 Definitions

Vascular access events included arteriovenous fistula thrombosis and stenosis. Arteriovenous fistula thrombosis was defined as visible thrombus on ultrasound. Arteriovenous fistula stenosis was defined as stenotic vessel diameter $< 50\%$ of the diameter of the adjacent relatively normal vessel [9], combined with the following clinical manifestations: (1) natural blood flow < 500 mL/min; (2) inability to meet the blood flow required by the dialysis prescription; (3) elevated dialysis venous pressure; (4) difficult puncture; (5) decreased dialysis adequacy; and (6) abnormal physical signs of the fistula.

1.4 Follow-up and Grouping

The follow-up cutoff date was September 15, 2021. The endpoint events were occurrence of vascular access events (arteriovenous fistula stenosis or thrombosis) or patient death. Patients were divided into four groups based on MPV quartiles: Q1 group (MPV: 6.1–8.1 fL), Q2 group (MPV: 8.2–8.8 fL), Q3 group (MPV: 8.9–9.6 fL), and Q4 group (MPV: 9.7–14.1 fL). General conditions, laboratory tests, and incidence rates of arteriovenous fistula thrombosis and stenosis were compared among the four groups.

1.5 Statistical Analysis

Statistical analysis was performed using SPSS 25.0 software and R version 4.3. Normally distributed continuous data with homogeneity of variance were expressed as mean $\pm$ standard deviation, with intergroup comparisons using ANOVA. Non-normally distributed data were analyzed using Mann-Whitney U nonparametric tests and expressed as median (P25, P75). Categorical data were expressed as [cases (%)], with intergroup comparisons using ^{2} tests. Kaplan-Meier survival curves were used to analyze vascular access event incidence in MHD patients, with Log-rank test for intergroup comparisons. Multiple Cox proportional hazard regression models were used to analyze the correlation between MPV and vascular access event risk, with hazard ratios (HR) and 95% con-

fidence intervals (95%CI) calculated. Subgroup analyses were further performed based on age, sex, dialysis vintage, hypertension, diabetes, platelet count, and hemoglobin. $P < 0.05$ was considered statistically significant.

Results

2.1 Clinical Data

This study included 343 MHD patients. During the 12-month follow-up period, 12 patients died, 3 underwent kidney transplantation, and 6 transferred to other dialysis centers (though their data remained collectible). There were no statistically significant differences in general characteristics among the four groups ($P > 0.05$). No significant differences were observed in hemoglobin, serum potassium, carbon dioxide, serum phosphorus, serum calcium, iPTH, albumin, β_2-microglobulin, or CRP among the four groups ($P > 0.05$). However, platelet count and mean platelet volume differed significantly among groups ($P < 0.05$), as shown in Tables 1 and 2 .

2.2 Kaplan-Meier Survival Analysis of Vascular Access Event Incidence

During follow-up, 60 patients (17.5%) experienced vascular access events, including 19 (5.5%) with arteriovenous fistula thrombosis and 41 (12.2%) with arteriovenous fistula stenosis. Kaplan-Meier analysis with MPV as a categorical variable showed statistically significant differences in vascular access event incidence among the four groups ($^2 = 25.691$, $P < 0.05$). The Q4 group had the highest incidence at 33.7%, followed by Q3 (17.8%) and Q2 (12.2%), while the Q1 group had the lowest incidence at 5.9% (Figure 1 [Figure 1: see original paper]).

2.3 Cox Proportional Hazard Regression Analysis of MPV and Vascular Access Event Risk

Using the occurrence of vascular access events (assignment: yes = 1, no = 0) as the dependent variable and MPV level (assignment: actual value) and MPV grouping (assignment: Q1 = 1, Q2 = 2, Q3 = 3, Q4 = 4) as independent variables, Cox proportional hazard regression analysis was performed. Model 1 adjusted for age, sex, and dialysis vintage, showing that elevated MPV level was a risk factor for vascular access events (HR = 1.58, 95%CI = 1.32–1.90, $P < 0.001$), with risk increasing as MPV levels rose (P for trend < 0.001). Model 2 further adjusted for hypertension, diabetes, erythropoiesis-stimulating agent (ESA) use, and antiplatelet drug use, confirming that elevated MPV remained a risk factor (HR = 1.69, 95%CI = 1.39–2.06, $P < 0.001$). Considering significant differences in platelet count among groups and that high hemoglobin level is a risk factor for arteriovenous fistula thrombosis, Model 3 additionally adjusted for platelet count and hemoglobin level, demonstrating that elevated MPV level

remained a risk factor for vascular access events (HR = 1.59, 95%CI = 1.28–1.97, P < 0.001) (Table 3).

2.4 Subgroup Analysis

To examine the stability of the relationship between MPV and vascular access events in MHD patients, stratified subgroup analyses were performed based on age, sex, dialysis vintage, hypertension, diabetes, ESA use, antiplatelet drug use, hemoglobin, and platelet count. No interactions were observed in any subgroups except for diabetes stratification (P for interaction = 0.022) (Figure 2 [Figure 2: see original paper]). Analysis of dialysis vintage between diabetic and non-diabetic groups showed that the non-diabetic group had significantly higher dialysis vintage than the diabetic group (P < 0.001).

Discussion

This study primarily investigated the relationship between MPV levels and vascular access event risk in MHD patients. Kaplan-Meier analysis demonstrated that high MPV was associated with increased vascular access event incidence. Multivariate Cox proportional hazard regression analysis showed that after adjusting for multiple factors, elevated MPV level remained a risk factor for vascular access events in MHD patients, with risk increasing as MPV levels rose. Subgroup analysis indicated that the correlation between high MPV and increased vascular access event incidence in MHD patients was stable.

Vascular access events mainly include arteriovenous fistula stenosis and thrombosis. Platelets play a role in the development of vascular access stenosis, which is primarily characterized by progressive neointimal hyperplasia caused by intimal injury. Platelets are involved in intimal hyperplasia through mechanisms such as shear stress, hypoxic injury, inflammation, and thrombosis associated with arteriovenous access creation [24]. Platelets with high MPV contain denser α-granules, aggregate faster after stimulation with adenosine diphosphate (ADP) or collagen, and secrete platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β) [25], fibrinogen, and β-thromboglobulin [3]. PDGF and TGF-β are two important factors causing intimal hyperplasia and are highly expressed in the intima of arteriovenous fistula stenosis [24,26]. Additionally, platelets play a crucial role in thrombus formation, with activated platelets increasing thrombotic risk. Patients with vascular access dysfunction exhibit higher platelet aggregability [27]. Arteriovenous fistula stenosis is the most common vascular access event (accounting for up to 90%), limiting blood flow and potentially leading to thrombosis and loss of fistula function [28].

Previous studies have shown that age, diabetes, male sex, and cardiovascular disease are associated with vascular access events in hemodialysis patients [29-30]. To further confirm the relationship between MPV and vascular access events in MHD patients, this study performed subgroup analyses of factors that may affect fistula stenosis, including age, sex, and diabetes. Except for diabetes

stratification, no statistically significant interactions were observed in other stratifications. Although interaction was found when stratifying by diabetes status, the non-diabetic group had higher dialysis vintage than the diabetic group, suggesting this may be influenced by dialysis vintage. Subgroup analysis indicates that the correlation between high MPV and increased vascular access event incidence in MHD patients is stable.

Despite various monitoring techniques for identifying vascular access dysfunction, results are affected by numerous variables, most importantly vascular access type, puncture technique, and operator influence [10]. MPV is a clinical indicator considered an important marker of platelet activity [11-12]. High MPV levels have been reported to be associated with various cardiovascular and cerebrovascular embolic diseases [13-16]. The Tromsø Study found that elevated MPV is a predictor of venous thromboembolism [6]. A meta-analysis showed that MPV levels were significantly higher in patients with deep vein thrombosis, with a diagnostic odds ratio of 4.76 and accuracy of 0.66 at a cutoff of 8.29 fL [17]. In the general population, MPV is recognized as a factor predicting thrombosis, thromboembolism, and adverse cardiovascular outcomes [6,18-23].

Our findings suggest that MPV may serve as a biomarker for vascular access events in MHD patients, helping clinicians identify high-risk populations early. Study limitations include: not distinguishing fistula location (forearm or upper arm) and puncture technique (heterogeneity in our center), which are two important factors for stenosis or thrombosis risk [31-32]; this being a single-center study with limited sample size; and potential regional and methodological differences that may yield different results from other studies. To reduce such bias, more multicenter large-scale studies are needed.

In summary, this study demonstrates through Kaplan-Meier analysis that high MPV is associated with increased vascular access event incidence. Multivariate Cox proportional hazard regression analysis shows that after adjusting for multiple factors, elevated MPV level remains a risk factor for vascular access events in MHD patients, with risk increasing as MPV levels rise. Subgroup analysis confirms the stability of this correlation. This study provides evidence that MPV may be a biomarker for arteriovenous fistula vascular access events in MHD patients, helping clinicians identify high-risk populations, enhance monitoring, and enable timely intervention.

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Author Contributions

ZHU Rongfang and JIN Jingjing designed the study; LIANG Xiangnan performed statistical analysis; QIAN Yuetong conducted arteriovenous fistula ultrasound monitoring; ZHU Rongfang and GENG Tonghui collected data; ZHU Rongfang wrote the manuscript; BAI Yaling and XU Jinsheng reviewed and edited the manuscript.

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Note: Figure translations are in progress. See original paper for figures.