Journal of Inflammation Research

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ORIGINAL RESEARCH

The Simplified Thrombo-Inflammatory Score as a Novel Predictor of All-Cause Mortality in Patients with Heart Failure: A Retrospective Cohort Study

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Background: The simplified thrombo-inflammatory score (sTIPS) has recently emerged as a novel prognostic score. Hence, we investigated the prognostic value of sTIPS for predicting long-term mortality in patients with heart failure (HF).

Methods: A total of 3741 patients were analyzed in this study. The sTIPS was calculated based on the white blood cell count (WBC) and the mean platelet volume to platelet count (MPV/PC) ratio at admission. The mean follow-up time was 22.75 months. Multivariable Cox regression analyses were used to investigate the associations between the sTIPS and all-cause mortality (ACM).

Results: In the whole study population, multivariate Cox regression analysis showed that patients in both the sTIPS 2 and sTIPS 1 groups had significantly increased risk of ACM as compared with patients in the sTIPS 0 group (hazard ratio [HR]=1.706, 95% confidence interval [CI]: 1.405–2.072, P<0.001 and HR = 1.431, 95% CI 1.270–1.612, P<0.001). The same significant trend was observed in heart failure with preserved ejection fraction (HFpEF) patients (sTIPS1 vs sTIPS0: HR = 1.366, 95% CI 1.100–1.697, P = 0.005; sTIPS2 vs sTIPS0: HR = 1.995, 95% CI 1.460–2.725, P<0.001). However, only sTIPS 1 group had a significantly increased the risk of ACM compared to the sTIPS 0 group among patients with HFmrEF (sTIPS1 vs sTIPS0: HR = 1.648, 95% CI 1.238–2.194, P = 0.001) and HFrEF (sTIPS1 vs sTIPS0: HR = 1.322, 95% CI 1.021–1.712, P = 0.035).

Conclusion: sTIPS is useful in predicting risk for long-term mortality in patients with HF.

Keywords: simplified thrombo-inflammatory score, heart failure, prognosis, all-cause mortality

Introduction

HF is a progressive clinical syndrome caused by abnormal cardiac structure or function in which patients have typical symptoms such as breathlessness, ankle swelling, and fatigue, as well as clinical signs related to an abnormality of cardiac structure or function.[1] HF is a major and growing public health problem, with its high morbidity and mortality causing heavy economic burden.[2] Despite significant improvements in treatment and survival of HF, prognosis remains poor.[3] Thus, precise risk stratification and early identification of modifiable risk factors are crucial for improving outcomes in patients with HF. Several biomarkers had been reported for predicting clinical prognosis of HF patients, such as N-terminal pro B-type natriuretic peptide (NT-proBNP),[4] uric acid (UA),[5] WBC,[6] serum cholesterol levels,[7] PC,[8] MPV[9] and so on. However, the pathogenesis and pathophysiological features of HF are complicated and heterogeneous, and a single index cannot accurately predict disease severity and prognosis in HF patients. In recent years, the risk stratification scores that is based on multiple clinical variables provide novel insights into prognostic stratification of

Received: 30 November 2023
Accepted: 8 March 2024
Published: 20 March 2024

cardiovascular diseases(CVD), for example, Intermountain Risk Score,[10,11] Naples Score,[12] ABC score,[13] etc. These have provided the possible approaches to develop a reliable prognostic model for HF patients.

Both inflammation and thrombosis play an essential role in the development and progression of HF.[14] It is well - established that inflammation and thrombosis are interdependent. Inflammation can induce thrombosis, and thrombosis can further aggravate the development of inflammation.[15] Therefore, these two key pathophysiologic processes are proposed to be studied and managed as a common entity under the concept of thrombus inflammation. Recently, sTIPS, a novel prognostic score based on thrombo-inflammatory status, has been introduced.[16] The sTIPS combines the predictive information derived from platelet function/count and leukocyte count. Previous study has demonstrated that sTIPS is useful in predicting worse immediate and long-term outcomes following ST-elevation myocardial infarction.[17] However, it has not been verified in patients with HF. Therefore, we investigated whether sTIPS is able to predict long-term mortality of patients with HF in a large retrospective study.

Methods

This is a single-center, retrospective cohort study, to investigate the relationship between sTIPS and long-term mortality risk in patients with HF. The study complies with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of The First Affiliated Hospital of Xinjiang Medical University. A flowchart of the study design is shown in Figure 1.

Patient Selection and Endpoint

A total of 4442 patients with HF admitted to the First Affiliated Hospital of Xinjiang Medical University from November 2012 to December 2021 were continuously recruited. The inclusion criteria included patients with previously diagnosed and medically treated HF [New York Heart Association (NYHA) class II–IV]. The exclusion criteria were sepsis or shock from any cause on admission to hospital, malignancy, autoimmune diseases, severe liver dysfunction (alanine aminotransferase or total bilirubin levels over 3 times the upper limit of normal), corticosteroid therapy, acute or chronic inflammatory diseases, and incompleteness of their medical profiles. Finally, 3741 patients with HF were

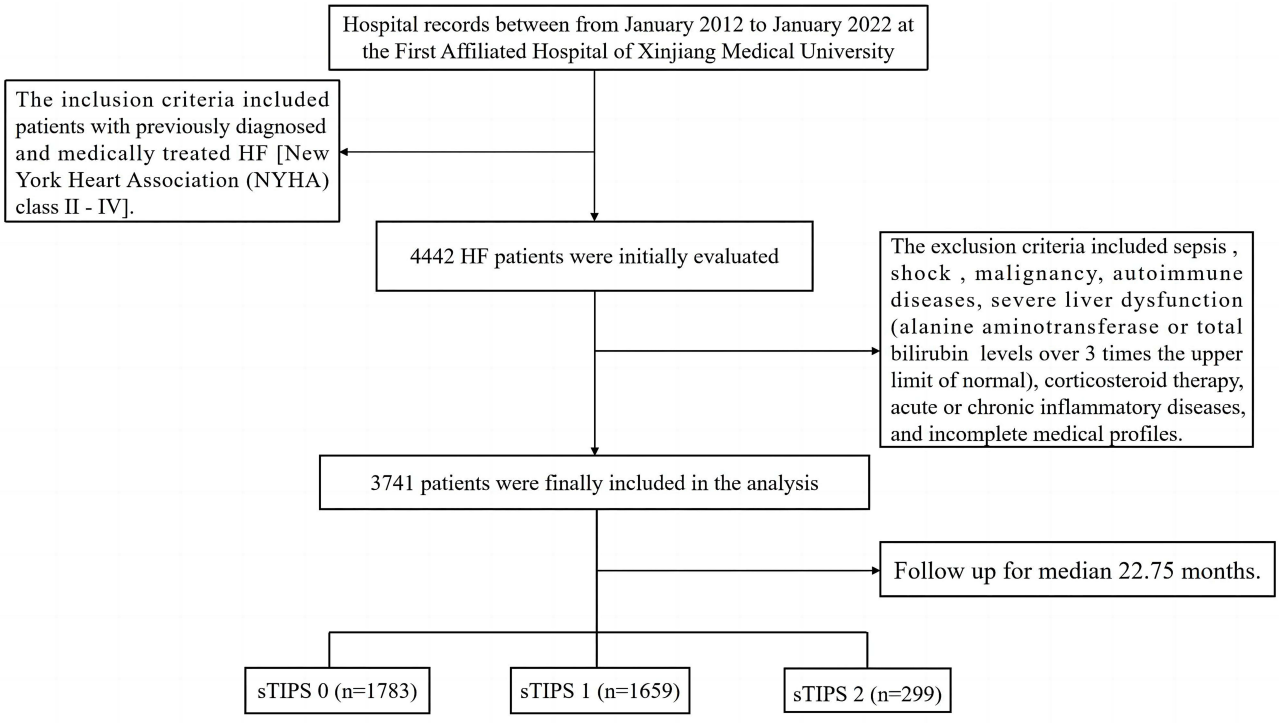

Figure 1 Flowchart of patient enrollment.

enrolled in this study. Based on the measurement of left ventricular ejection fraction (LVEF), these patients were categorized in HFpEF(LVEF≥50%), Heart failure with mid - range ejection fraction (HFmrEF, LVEF 40–50%) and Heart failure with reduced ejection fraction (HFrEF, LVEF ≤ 40%).[3] The primary endpoint was ACM.

Data Collection

The baseline demographic, clinical and laboratory data were obtained from detailed medical records taken during the hospital admission. These included demographic data (age, gender, etc.), past medical history (diabetes mellitus, hypertension, coronary artery disease (CAD), valvular heart disease (VHD), congenital heart disease (CHD), cardiomyopathy (CM), etc.), results of blood tests and drug treatments. Peripheral blood samples of patients were collected from fasting state early in the morning after admission. Baseline laboratory data containing blood routine, blood lipid profile, NT-proBNP, hepatic and renal function were measured strictly according to operational procedures by professionals in standard basic laboratory.

sTIPS Score and Research Groups

sTIPS was calculated based on the methodology proposed by Li et al.[16] Receiver-operating characteristic (ROC) curves were used to determine the discrimination thresholds of admission WBC (cutoff: 8.4×10^9/L) and MPV/PC (cutoff: 7.31 10^2fL/10^9L^{-1}) for predicting mortality in our study population. Based on these cut-off values, patients with both a high WBC and a high MPV/PC ratio were assigned a score of 2, while patients showing elevations in only one or neither marker were assigned scores of 1 and 0, respectively.

Follow-Up

In our study, all patients received regular follow-up by office visits or by telephone interview. The patients were followed up for at least 1 year, and the longest follow-up time was 10 years. Drug compliance and adverse events were evaluated at each follow-up.

Statistical Analyses

All analyses were performed using the SPSS 24.0 for Windows statistical software. Continuous data are presented as the mean ± standard deviation or the median (top, bottom quartile). Categorical data are presented as the frequencies and percentages. For comparison of baseline data, continuous variables were compared using analysis of variance or Student's *t*-test for normally distributed variables and Kruskal–Wallis test or Mann–Whitney *U*-test for non-normally distributed variables. The Chi-squared test (χ^2) was used to compare categorical variables. Multivariate Cox regression analysis was used for determination of independent parameters for prognosis. Long-term survival was analyzed using the Kaplan-Meier method. *HR* and 95% *CI* were calculated, and a P value less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

Table 1 shows the baseline characteristics of the 3741 HF patients. Patients with elevated sTIPS were older and had higher rates of VHD, but lower rates of CAD, hypertension, and cardiomyopathy. In addition, patients with higher sTIPS had a less use of angiotensin receptor-neprilysin inhibitor (ARNI), β-blocker, mineralocorticoid receptor antagonist (MAR), and sodium-glucose cotransport 2 inhibitors (SGLT2i). Given sTIPS formula, there were obvious differences in leukocyte and platelet parameters. sTIPS was positively correlated with WBC and MPV (P <0.001), but negatively correlated with PC (P <0.001). Meanwhile, other laboratory indices, including albumin (ALB), total bilirubin (TBIL), creatinine (Cr), UA, lipid profiles, and NT-proBNP, were also significantly different among the three sTIPS groups (all P-values <0.05).

The baseline characteristics of patients with HFrEF, HFmrEF and HFpEF were then analyzed separately (Table 2). In these three types of HF patients, several laboratory indices, such as WBC, PC, MPV, TBIL, Cr, UA and NT-proBNP,

Table 1 Baseline Characteristics in All HF Patients

Variables	sTIPS0 (n=1783)	sTIPS1 (n=1659)	sTIPS2 (n=299)	P value
Age (years)	63.78±13.35	64.75±14.06	67.32±14.00	**<0.001**
Male (n,%)	1166 (65.4)	1088 (65.6)	187 (62.5)	0.587
CAD (n,%)	993 (55.7)	1008 (60.1)	146 (48.8)	**<0.001**
Hypertension (n,%)	954 (53.5)	875 (52.7)	123 (41.1)	**<0.001**
Diabetes (n,%)	459 (25.7)	461 (27.8)	76 (25.4)	0.353
VHD (n,%)	396 (22.2)	319 (19.2)	78 (26.1)	**0.010**
CHD (n,%)	36 (2.0)	32 (1.9)	6 (2.0)	0.981
CM (n,%)	294 (16.5)	203 (12.2)	27 (9.0)	**<0.001**
WBC ($\times 10^9$/L)	6.55±1.25	11.00±10.90	13.20±12.98	**<0.001**
PC ($\times 10^9$/L)	241.49±78.00	243.35±112.01	103.15±27.62	**<0.001**
MPV (fL)	10.47±1.13	10.89±1.44	11.65±2.00	**<0.001**
ALB (g/L)	38.31±4.93	37.63±5.08	36.91±5.60	**<0.001**
TBIL (μmol/L)	14.20 (9.50, 20.70)	16.28 (9.70, 26.30)	30.10 (13.88, 58.38)	**<0.001**
Cr (μmol/L)	84.30 (70.23, 98.44)	91.00 (75.00, 121.23)	96.92 (85.40, 203.50)	**<0.001**
UA(μmmol/L)	403.00 (316.72, 514.90)	424.73 (324.86, 552.98)	515.30 (353.43, 704.01)	**<0.001**
TG (mmol/L)	1.24 (0.91, 1.80)	1.3(0.95, 1.85)	1.36 (0.98, 2.24)	**0.015**
TC (mmol/L)	3.71±1.09	3.68±1.14	3.44±1.18	**0.003**
HDL-C (mmol/L)	0.98±0.31	0.96±0.33	0.90±0.51	**0.001**
LDL-C (mmol/L)	2.40±0.88	2.37±0.93	2.18±0.95	**0.003**
NT-proBNP (pg/mL)	1913.00 (617.75, 5470.00)	3230.00 (898.00, 7963.50)	7220.00 (2072.00, 10,642.50)	**<0.001**
ARNI (n,%)	471 (31.3)	338 (26.0)	37 (17.4)	**<0.001**
β-blocker (n,%)	659 (43.7)	453 (34.8)	52 (24.4)	**<0.001**
Diuretics (n,%)	180 (12.0)	149 (11.5)	17 (8.0)	0.234
MAR (n,%)	331 (22.0)	234 (18.0)	25 (11.7)	**<0.001**
SGLT2i (n,%)	124 (8.3)	92 (7.1)	7 (3.3)	**0.029**

Notes: P value for the comparison among the three groups. The boldfaced P values are statistically different.

Abbreviations: sTIPS, simplified thrombo-inflammatory prognostic score; CAD, coronary artery disease; VHD, valvular heart disease; CHD, congenital heart disease; CM, cardiomyopathy; WBC, white blood cell count; PC, platelet count; MPV, mean platelet volume; ALB, Albumin; TBIL, total bilirubin; Cr, Creatinine; UA, Uric acid; TG, Triglyceride; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; ARNI, angiotensin receptor-neprilysin inhibitor; MAR, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransport 2 inhibitors.

were significantly different among the three sTIPS groups (all *P*-values <0.05). In addition, other variables were significantly different among the three sTIPS groups in the HFpEF patients. These variables included CAD, Hypertension, VHD, ALB, high-density lipoprotein cholesterol (HDL-C), use of ARNI, β-blocker and MAR. In the HFmrEF patients, we also found that age, CAD, CM and HDL-C were significantly different among the three sTIPS groups.

STIPS and Long-Term Mortality

In the overall population, the long-term mortality rate gradually increased as sTIPS increased (sTIPS 0 vs.1 vs 2: 35.7% vs 46.5% vs 65.2%, *P* <0.001). Similarly, the same tendency was observed among HFrEF, HFmrEF and HFpEF subgroups, as shown in Table 3. Furthermore, as shown in Figure 2, the Kaplan-Meier survival analysis suggested that the cumulative mortality rate was significantly greater in patients with higher sTIPS (Log-rank *P* <0.001).

Multivariate Cox regression analysis models were further performed to assess whether there was a significant correlation between the sTIPS and long-term mortality in patients with HF. After adjusting for the traditional clinical prognostic factors including gender, age, TBIL, Cr, UA, ALB, TG, TC, HDL-C and low-density lipoprotein cholesterol, we found that high sTIPS showed a positive association with the risk of mortality. In all HF patients, patients in both the sTIPS 2 and sTIPS 1 group had a significantly increased the risk of long-term ACM compared to the sTIPS 0 group (sTIPS1 vs sTIPS0: HR = 1.431, 95% CI 1.270–1.612, P <0.001; sTIPS2 vs sTIPS0: HR = 1.706, 95% CI 1.405–2.072, P<0.001). The same significant trend was observed in HFpEF patients (sTIPS1 vs sTIPS0: HR = 1.366, 95% CI 1.100–

Table 2 Baseline Characteristics in the Subgroups of Patients

Variables	HFpEF				HFmrEF				HFrEF			
	sTIPS0 (n=567)	sTIPS1 (n=569)	sTIPS2 (n=122)	P value	sTIPS0 (n=336)	sTIPS1 (n=325)	sTIPS2 (n=44)	P value	sTIPS0 (n=363)	sTIPS1 (n=307)	sTIPS2 (n=45)	P value
Age (years)	66.27±13.33	65.50±14.23	66.89±14.64	0.482	62.52±12.42	65.39±13.21	65.82±12.45	**0.010**	60.59±12.53	60.71±13.92	64.93±13.89	0.110
Male (n,%)	244 (43.0)	247 (43.4)	53 (43.4)	0.991	107 (31.8)	97 (29.8)	15 (34.1)	0.775	275 (75.8)	237 (77.2)	32 (71.1)	0.656
CAD (n,%)	305 (53.8)	343 (60.3)	55 (45.1)	**0.004**	206 (61.3)	229 (70.5)	28 (63.6)	**0.044**	195 (53.7)	168 (54.7)	24 (53.3)	0.961
Hypertension (n,%)	359 (63.3)	332 (58.3)	61 (50.0)	**0.016**	180 (53.6)	170 (52.3)	16 (36.4)	0.098	167 (46.0)	140 (45.6)	17 (37.8)	0.574
Diabetes (n,%)	156 (27.5)	148 (26.0)	29 (23.8)	0.659	86 (25.6)	108 (33.2)	13 (29.5)	0.098	78 (21.5)	80 (26.1)	11 (24.4)	0.379
VHD (n,%)	142 (25.0)	121 (21.3)	39 (32.0)	**0.031**	61 (18.2)	56 (17.2)	8 (18.2)	0.950	80 (22.0)	59 (19.2)	13 (28.9)	0.292
CHD (n,%)	16 (2.8)	15 (2.6)	3 (2.5)	0.967	4 (1.2)	2 (0.6)	1 (2.3)	0.512	7 (1.9)	3 (1.0)	1 (2.2)	0.565
CM (n,%)	32 (5.6)	22 (3.9)	3 (2.5)	0.181	52 (15.5)	29 (8.9)	3 (6.8)	**0.019**	121 (33.3)	99 (32.2)	13 (28.9)	0.824
WBC (×109/L)	6.56±1.27	10.83±10.87	12.44±12.21	**<0.001**	6.55±1.23	10.61±9.48	10.45±5.17	**<0.001**	6.59±1.20	9.84±8.49	12.53±11.48	**<0.001**
PC (×109/L)	241.89±73.05	248.80±113.86	99.46±24.59	**<0.001**	252.36±101.66	242.17±110.55	106.59±29.53	**<0.001**	232.06±64.50	241.22±112.74	105.71±28.53	**<0.001**
MPV (fL)	10.40±1.15	10.80±1.42	11.53±2.10	**<0.001**	10.45±1.07	10.92±1.47	11.17±1.97	**<0.001**	10.57±1.11	10.99±1.44	12.07±1.87	**<0.001**
ALB (g/L)	38.50±4.50	37.75±4.95	37.12±5.33	**0.004**	38.74±5.18	38.23±4.75	38.47±5.25	0.438	38.97±4.81	38.88±4.48	39.13±4.74	0.934
TBIL (μmol/L)	12.65 (9.17, 18.80)	14.42 (9.32, 25.45)	26.30 (9.92, 56.9)	**<0.001**	13.08 (9.02, 17.64)	14.91 (9.48, 23.69)	31.40 (12.48, 54.24)	**<0.001**	16.63 (10.90, 25.88)	19.31 (12.27, 30.77)	35.38 (18.58, 63.75)	**<0.001**
Cr (μmol/L)	82.50 (68.65, 97.98)	88.00 (73.00, 99.20)	93.61 (80.99, 108.93)	**<0.001**	82.42 (69.03, 98.97)	89.96 (72.91, 121.15)	96.17 (87.07, 167.68)	**<0.001**	86.12 (73.00, 96.00)	92.50 (78.79, 100.44)	98.69 (90.73, 266.11)	**<0.001**
UA (μmmol/L)	376.00 (296.55, 474.84)	391.00 (308.40, 497.00)	444.82 (295.69, 614.72)	**0.026**	385.95 (312.40, 488.84)	435.00 (324.65, 563.01)	558.77 (415.67, 679.62)	**<0.001**	471.00 (379.14, 582.00)	487.76 (366.50, 644.40)	612.96 (440.65, 813.54)	**0.004**
TG (mmol/L)	1.31 (0.95, 2.06)	1.31 (0.96, 2.01)	1.48 (0.99, 2.39)	0.092	1.49 (0.98, 2.32)	1.39 (1.00, 1.91)	1.23 (0.93, 1.71)	0.064	1.55±1.12	1.43±0.85	1.45±0.85	0.371
TC (mmol/L)	3.82±1.14	3.74±1.22	3.51±1.26	0.064	3.69±1.07	3.63±1.11	3.38±0.94	0.303	3.68±1.07	3.60±1.05	3.35±1.16	0.161
HDL-C (mmol/L)	1.04±0.33	0.98±0.33	0.97±0.63	**0.023**	1.00±0.30	0.97±0.31	0.83±0.28	**0.009**	0.91±0.26	0.93±0.30	0.91±0.29	0.759
LDL-C (mmol/L)	2.42±0.90	2.41±0.99	2.19±1.00	0.084	2.37±0.93	2.30±0.96	2.15±0.77	0.385	2.44±0.85	2.35±0.85	2.14±0.98	0.081
NT-proBNP (pg/mL)	953.00 (279.00, 3370.00)	1720.00 (712.15, 5750.00)	5042.50 (970.50, 9452.00)	**<0.001**	1360.00 (494.00, 4783.00)	3203.50 (836.75, 8315.00)	8090.0 (4966.0, 10,000.5)	**<0.001**	3924.00 (1547.50, 7025.50)	4720.00 (2556.50, 78,381.00)	7957.50 (4093.00, 13,566.00)	**<0.001**
ARNI (n,%)	117 (23.9)	91 (19.4)	11 (12.6)	**0.033**	107 (36.6)	73 (29.1)	10 (28.6)	0.149	126 (42.1)	87 (36.9)	10 (3.5)	0.394
β-blocker (n,%)	220 (45.0)	167 (35.6)	20 (23.0)	**<0.001**	134 (45.9)	95 (37.8)	13 (37.1)	0.140	141 (47.0)	88 (37.1)	11 (37.9)	0.063
Diuretics (n,%)	43 (8.8)	44 (9.4)	4 (4.6)	0.344	37 (12.7)	34 (13.5)	5 (14.3)	0.936	52 (17.4)	42 (17.8)	6 (20.7)	0.906
MAR (n,%)	85 (17.4)	75 (16.0)	5 (5.7)	**0.023**	73 (25.0)	49 (19.5)	7 (20.0)	0.293	84 (28.0)	65 (27.5)	8 (27.6)	0.993
SGLT2i (n,%)	20 (4.1)	18 (3.8)	2 (2.3)	0.725	29 (9.9)	20 (8.0)	1 (2.9)	0.326	39 (13.1)	33 (14.0)	3 (10.3)	0.843

Notes: P value for the comparison among the three groups. The boldfaced P values are statistically different.

Abbreviations: sTIPS, simplified thrombo-inflammatory prognostic score; HFpEF, Heart failure with preserved ejection fraction; HFmrEF, Heart failure with mid - range ejection fraction; HFrEF, Heart failure with reduced ejection fraction; CAD, coronary artery disease; VHD, valvular heart disease; CHD, congenital heart disease; CM, cardiomyopathy; WBC, white blood cell count; PC, platelet count; MPV, mean platelet volume; ALB, Albumin; TBIL, total bilirubin; Cr, Creatinine; UA, Uric acid; TG, Triglyceride; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; ARNI, angiotensin receptor-neprilysin inhibitor; MAR, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransport 2 inhibitors.

https://doi.org/10.2147/JIR.S452544 DovePress

Table 3 Long-Term ACM in All Patients and in the Subgroups of Patients

Groups	ACM (n,%)			
	sTIPS0	sTIPS1	sTIPS2	P value
All patients	636 (35.7)	772 (46.5)	195 (65.2)	**<0.001**
HFpEF	188 (33.2)	229 (40.2)	72 (59.0)	**<0.001**
HFmrEF	96 (28.6)	149 (45.8)	23 (52.3)	**<0.001**
HFrEF	136 (37.5)	143 (46.6)	28 (62.2)	**0.002**

Notes: P value for the comparison among the three groups. The boldfaced P values are statistically different.

Abbreviations: ACM, all-cause mortality; sTIPS, simplified thrombo-inflammatory prognostic score; HFpEF, Heart failure with preserved ejection fraction; HFmrEF, Heart failure with mid - range ejection fraction; HFrEF, Heart failure with reduced ejection fraction.

1.697, P = 0.005; sTIPS2 vs sTIPS0: HR = 1.995, 95% CI 1.460–2.725, P<0.001). However, only sTIPS 1 group had a significantly increased the risk of ACM compared to the sTIPS 0 group among patients with HFmrEF (sTIPS1 vs sTIPS0: HR = 1.648, 95% CI 1.238–2.194, P = 0.001) and HFrEF (sTIPS1 vs sTIPS0: HR = 1.322, 95% CI 1.021–1.712, P = 0.035). The data are shown in Table 4.

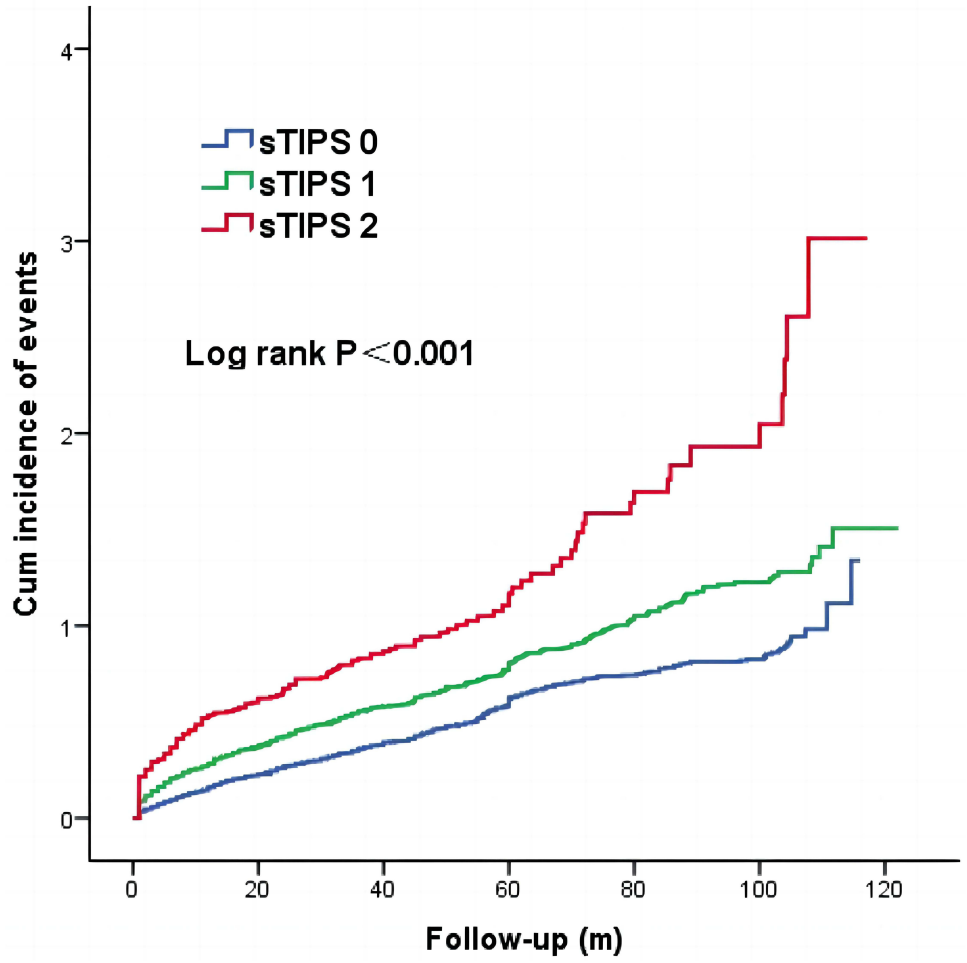

Figure 2 Kaplan-Meier curves for survival analysis of all-cause mortality in all HF patients.

Table 4 Multivariable Cox Regression Analysis Results for Long-Term ACM in All Patients and in the Subgroups of Patients

Variables	All patients			HFpEF			HFmrEF			HFrEF		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Gender (male)	1.103	(0.982–1.238)	0.098	1.164	(0.956–1.418)	0.131	1.242	(0.929–1.660)	0.143	1.218	(0.919–1.615)	0.171
Age (years)	1.032	(1.027–1.037)	**<0.001**	1.041	(1.032–1.050)	**<0.001**	1.038	(1.026–1.050)	**<0.001**	1.032	(1.021–1.043)	**<0.001**
TBIL	1.004	(1.003–1.005)	**<0.001**	1.005	(1.002–1.007)	**<0.001**	1.002	(0.999–1.006)	0.210	1.018	(1.010–1.026)	**<0.001**
Cr	1.000	(1.000–1.000)	0.195	1.000	(1.000–1.000)	0.238	1.000	(1.000–1.000)	0.436	1.000	(1.000–1.000)	0.381
UA	1.000	(1.000–1.000)	0.027	1.000	(1.000–1.000)	0.148	1.000	(1.000–1.000)	0.872	1.000	(1.000–1.000)	0.743
ALB	0.949	0.938–0.960)	**<0.001**	0.932	(0.912–0.952)	**<0.001**	0.949	(0.921–0.978)	**0.001**	0.958	(0.930–0.986)	**0.004**
TG	1.007	(0.980–1.034)	0.629	1.012	(0.979–1.046)	0.473	1.330	(0.881–1.122)	0.232	0.816	(0.665–1.003)	0.053
TC	1.114	(0.956–1.299)	0.167	1.004	(0.776–1.299)	0.974	0.994	(0.834–2.121)	0.922	1.751	(1.103–2.781)	**0.018**
HDL-C	0.498	(0.403–0.614)	**<0.001**	0.579	(0.412–0.814)	**0.002**	0.794	(0.132–0.430)	0.393	0.566	(0.318–1.008)	0.053
LDL-C	0.877	(0.734–1.047)	0.146	1.013	(0.747–1.374)	0.934	0.238	(0.467–1.350)	**<0.001**	0.555	(0.342–0.902)	**0.017**
sTIPS1 vs sTIPS0	1.431	(1.270–1.612)	**<0.001**	1.366	(1.100–1.697)	**0.005**	1.648	(1.238–2.194)	**0.001**	1.322	(1.021–1.712)	**0.035**
sTIPS2 vs sTIPS0	1.706	(1.405–2.072)	**<0.001**	1.995	(1.460–2.725)	**<0.001**	1.470	(0.795–2.719)	0.220	1.232	(0.769–1.973)	0.386

Notes: P value for the comparison among the three groups. The boldfaced P values are statistically different.

Abbreviations: ACM, All-cause mortality; HFpEF, Heart failure with preserved ejection fraction; HFmrEF, Heart failure with mid - range ejection fraction; HFrEF, Heart failure with reduced ejection fraction; HR: Hazard ratios; 95% CI: 95% confidence interval; TBIL, total bilirubin; Cr, Creatinine; UA, Uric acid; ALB, Albumin; TG, Triglyceride; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; sTIPS, simplified thrombo-inflammatory prognostic score.

https://doi.org/10.2147/JIR.S452544

Discussion

The present study indicated that sTIPS, which combines the inflammatory markers (WBC) and thrombotic markers (MPV/PC) in routine blood tests, may be able to identify high-risk HF patients in the early phase of admission and is an independent predictor of mortality risk in HF patients, especially in HFpEF patients. This is the first study to investigate the association between sTIPS and ACM in HF patients.

HF is frequently the final stage of numerous CVD and is linked to elevated rates of morbidity, mortality, and substantial healthcare costs.[18] Predicting the prognosis of HF early is essential in order to enable the implementation of timely interventions aimed at mitigating or halting disease progression and enhancing long-term outcomes. In our study, all data were based on real-world data. Further multivariate Cox analysis was conducted that focused on a total of 3741 patients with HF. The results suggest that sTIPS can predict the risk of long-term mortality in HF patients. Based on the most recent guidelines, it is evident that the three distinct classifications of HF (HFpEF, HFmrEF, and HFrEF) exhibit varying pathophysiological underpinnings underpinnings, necessitating unique approaches to both prevention and treatment.[3] So we performed a separate multivariate analysis for HFpEF, HFmrEF, and HFrEF patients. We found a similar trend in HFpEF patients as in the overall population, but only the sTIPS 1 group had a higher risk of ACM among the other two types of patients.

Furthermore, Multivariable Cox analyses in the entire study population found that common risk factors for CVD, like age, TBIL, ALB and HDL-C, are also risk factors for long-term mortality risk in HF, consistent with previous studies. Prior researches conducted across various populations has demonstrated that serum ALB is a significant independent predictor of long-term mortality in individuals with CVD.[19,20] Age is a widely recognized risk factor for long-term mortality in individuals with HF.[21] Elevated TBIL levels at admission are also linked to higher systolic blood pressure and increased risk of cardiac mortality in acute HF patients.[22] In addition, higher levels of HDL-C are linked to lower rates of cardiovascular events.[23]

In view of our present results, the high value of sTIPS may reflect both the increased systemic inflammatory response and excessive thrombotic state in HF patients. Inflammation and activation of the immune system significantly contribute to the progression of HF.[24] So far, several studies have shown that HF patients have elevated levels of circulating pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6.[25,26] Several inflammatory biomarkers have also been evaluated, assessing their usefulness as diagnostic and prognostic indicators in HF. Elevated plasma C-reactive protein (CRP) concentrations in patients with HF is associated with greater comorbidity burden and is considered an independent prognostic indicator of adverse events.[27,28] Previous studies have shown that the leucocytosis predicts an increased mortality and hospitalization rate in patients with HF.[6,29] Moreover, various leukocyte subpopulations are also closely related to poor prognosis in HF patients.[30] Leucocytes, as the effector and coordinator of the cellular inflammatory process, play an important role in the pathogenesis and prognosis of HF by contributing to inflammation, extracellular matrix remodelling, and myocardial fibrosis processes.[31]

The patients with HF have increased risk of venous thromboembolism, stroke, and sudden death.[32] The platelet activation and thrombus formation are major contributors to the development of severe cardiovascular complications. Patients with HF exhibit elevated levels of whole blood aggregation, MPV, and various platelet-derived adhesion molecules, such as soluble and platelet-bound P-selectin and soluble CD40 ligand.[33] Previous studies have highlighted the prognostic value of platelet markers in individuals with HF. Thrombocytopenia was associated with 1-year death in patients initially diagnosed as having HF with low ejection fraction, as Mojadidi et al demonstrated.[34] MPV, which represents platelet activation, was related to the risk of HF hospitalization in patients with chronic HF.[35] A study by Yamaguchi et al found that low platelet count was associated with poor prognosis in patients with acute HF, and PLT was significantly negatively correlated with MPV.[8]

Inflammation and thrombosis are closely linked. Inflammatory processes are regulated by platelet-induced activation of blood leukocytes.[14] Leukocytes can work in synergy with platelets to generate tissue factor, microparticles, and surfaces for thrombin to generate fibrin.[36] The complex interaction among innate immunity, platelet activation, and coagulation is commonly known as immunothrombosis.[37] Immunothrombosis can aggravate the development of disease and lead to the occurrence of adverse cardiovascular events.[37] Similarly, Immune-inflammation, platelet activation and

thrombus formation are interdependent in HF.[38] The utilization of solely inflammatory or thrombotic biomarkers is inadequate for comprehensively understanding the underlying pathophysiologic mechanisms of HF. Consequently, ongoing research is concentrating on strategies and markers that specifically target the interactions between platelets and leukocytes. The sTIPS, comprising of WBC and MPV/PC, combines both inflammatory and thrombotic information, and may serve as a more effective prognostic marker for HF compared to individual platelet or leukocyte parameters.

Our study is a large, single-center retrospective cohort study and all patients were followed up for a long time to predict the long-term adverse outcomes. However, the limitations of our study should also be mentioned. First, we only recorded the WBC and MPV/PC ratio at admission, but the changes in these markers at different time points were not recorded. Therefore, the effect of dynamic changes in these markers cannot be analyzed, and the ideal timing of sample collection for estimating risk stratification cannot be determined. Second, due to the lack of available data, we did not compare the sTIPS with other prognostic scoring systems, including GWTG-HF risk score[39] and CHA2DS2-Vasc score in the HF.[40] Third, our study mainly focused on a population study of HF patients in China, so the recommended cut-off values for WBC and MPV/PC ratio cannot be generalized to other populations. This presents a challenge to the broad adoption of sTIPS as a clinical marker. Last, our results need to be further verified by prospective, large-scale multicenter studies.

Conclusions

In summary, sTIPS may reflect the thrombo-inflammatory milieu in HF and was a strong predictor of long-term mortality in patients with HF. Thus, this score may be useful to help clinicians identify patients at high risk for HF and adapt an aggressive management plan and close monitoring.

Abbreviations

sTIPS, Simplified thrombo-inflammatory score; HF, Heart failure; WBC, White blood cell count; MPV, Mean platelet volume; PC, Platelet count; ACM, All-cause mortality; HFpEF, Heart failure with preserved ejection fraction; HFmrEF, Heart failure with mid - range ejection fraction; HFrEF, Heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; CAD, Coronary artery disease; CVD, Cardiovascular disease; VHD, Valvular heart disease; CHD, Congenital heart disease; CM, cardiomyopathy; ARNI, Angiotensin receptor-neprilysin inhibitor; MAR, Mineralocorticoid receptor antagonist; SGLT2i, Sodium-glucose cotransport 2 inhibitors; ALB, albumin; TBIL, total bilirubin; Cr, creatinine; UA, uric acid.

Data Sharing Statement

Due to confidentiality policies, data will not be shared.

Ethics Approval and Consent to Participate

The study protocol was approved by the Ethics Committee of The First Affiliated Hospital of Xinjiang Medical University. Due to the retrospective nature of our study, the requirement for written informed consent was waived by the ethics committee. The authors ensured that the data was anonymized and maintained with confidentiality.

Acknowledgments

The authors are grateful to the Department of Cardiology at the First Affiliated Hospital of Xinjiang Medical University for their help and expertise in conducting this study.

Funding

This work was supported by the Natural Science Foundation of Henan Province, National Natural Science Foundation of China, CORFCHDZ- Z, Henan Medical Science and Technique Foundation, (grant number 212300410072, 82000238).

Disclosure

The authors declare that they have no competing interests in this work.

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