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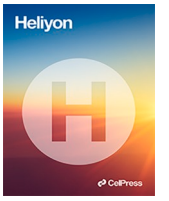

Research article

Diagnostic utility of HFLC% and IG% for acute Pancreatitis—A retrospective Case-Control study

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ABSTRACT

Objective: To evaluate the occurrence, development and outcome value of hyperfluorescent lymphocyte percentage (HFLC%) and immature granulocyte percentage (IG%) for acute pancreatitis (AP).

Methods: The laboratory data collected from 1533 patients diagnosed with AP between August 2018 and August 2022 were retrospectively analyzed. The patients were classified into mild acute pancreatitis (MAP) and non-mild acute pancreatitis (Non-MAP) groups; non-MAP groups were additionally subgrouped based on HFLC% at day 7. White blood cells (WBC), HFLC%, and IG% were examined from day 1 (baseline) to day 14 post-admission using Sysmex XN Series Hematology Analyzers. C-reactive protein (CRP), serum amylase (AMY), and lipase (LPS) were detected by Beckman AU5800.

Results: A total of 623 patients were finally included in the study [MAP group (n = 358) and Non-MAP group (n = 265)]. WBC, IG%, and CRP were higher in the Non-MAP group from day 1 to day 12 (all $P<0.05$). The HFLC% was not statistically significant from day 1 to day 6; yet, it increased on day 6 and 7 in the Non-MAP group. We divided patients in the Non-MAP group with complete data(101 patients) into HFLC% $\geq$ 2.9 %(31 patients) and HFLC% $<$ 2.9 %(70 patients) according to the threshold of 7th day HFLC%. WBC, HFLC%, IG%, and CRP effectively predicted the progression of MAP to Non-MAP (all $P < 0.001$). HFLC% was the most obvious value, followed by CRP and IG%. Combined with HFLC%, IG%,CRP and WBC in day7, the ROC analysis showed that the area under ROC curve of the combined indicators was the largest ($AUC = 0.912$, $P < 0.001$) and had higher sensitivity and specificity than single-item assessment of AP outcomes($P < 0.05$). HFLC% $<$ 2.9 %, IG% $>$ 1.7 %, CRP $>$28.66 mg/L, and WBC $>9.24 \times 10^9$/L indicated the possibility of AP disease aggravation. Also, HFLC% $<$2.9 % was directly associated with infection, SIRS, APPACHII grade, and ICU admission (all $P < 0.05$). In non-MAP there was a significant negative correlation between HFLC% and APACHE-II score ($r_s = -0.312$, $P = 0.023$).

Conclusion: HFLC% $<$2.9 % on 7th day was directly indicated more infection, systemic inflammatory response syndrome(SIRS), higher APPACH II grade and ICU admission. HFLC% may be an

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independent laboratory marker for prognosis in AP. Combining HFLC% with IG%, CRP, and WBC helps evaluate AP patients' disease development and outcome.

1. Introduction

Acute pancreatitis (AP) is a common inflammatory disease of the exocrine pancreas that causes severe abdominal pain and multiple organ dysfunction, which may lead to pancreatic necrosis and persistent organ failure, with a mortality of 1–5% [1]. Clinically, AP can be classified as mild acute pancreatitis (MAP), moderately severe acute pancreatitis (MSAP), and severe pancreatitis (SAP). MAP accounts for about 20%–25 % of all AP cases, and the progression from MAP to SAP occurs in about 9%–20 % of patients [2]. Delay in the diagnosis and treatment can further aggravate the patient's condition; thus, early diagnosis is extremely important. The diagnosis typically involves a combination of history and examination. Although inflammation markers [such as C-reactive protein (CRP), white blood cell count (WBC), blood amylase (AMY), lipase (LPS), etc.] and scoring systems (PANC3, Ranson, Acute Physiology and Chronic Health Evaluation [APACHE] II score, and Atlanta) have been continuously validated by scholars [3–5], there are still no ideal laboratory indicators for monitoring the disease progression.

With the introduction of the Sysmex XN series Hematology Analyzers, detecting hyperfluorescent lymphocyte percentage (HFLC%) and immature granulocyte percentage (IG%) has become simple, making it easier to obtain standardized data. HFLC is a new immune and inflammatory marker, an activated lymphocyte the organism produces after antigenic stimulation. This group of activated nucleic acid material is significantly increased and can bind more nucleic acid fluorescent dyes when entering the instrument for detection, resulting in increased fluorescence intensity of this group of lymphocytes. HFLC% is closely related to activated lymphocytes in peripheral blood and can reflect the activation of lymphocytes, including activated B and T lymphocytes and lymphocytes containing high RNA [6]. Morphologically, activated lymphocytes are described as having an increased size, an oval nucleus shape, and inlets and irregular contours [7]. The automated IG count, which enumerates granulocyte precursors (promyelocytes, myelocytes, and metamyelocytes), reflects the granulocytic left shift [8]. IG% in peripheral blood indicates bone marrow activation and severe infection and can predict the progression of early sepsis. In recent years, some studies have shown that IG% is a more effective and reliable marker than traditional inflammation markers such as WBC, neutrophil-to-lymphocyte ratio (NLR), and CRP in the early prediction of ANP [9]. These infantile granulocytes can be found in the peripheral blood of patients with infectious diseases, inflammation, sepsis, and hematological diseases. They are important in the diagnosis, treatment, and prognosis of diseases.

Current studies focus on the prediction of the severity of AP by inflammatory indicators, and the mortality rate of severe AP can reach 30 % [10]. Our retrospective study predicted the development and prognosis of AP by changes in HFLC% and IG% during hospitalization. The aim is to provide a more objective and sensitive laboratory index for clinical assessment of the prognosis of AP.

Table 1
Demographic data, etiology and comorbidity records of cases in AP study groups.

		MAP	Non-MAP
Number of patients (N)		358	265
Gender			
	Male	233	169
	Female	125	96
Median age(*M,IQR*)		47,18	48,23
Etiology			
	Biliary	152	113
	Hyperlipidemic	202	125
	Alcoholic	–	15
	Mixed type	–	6
	Idiopathic	4	6
Complication			
	Effusion of serous cavity	42	223
	Diabetic ketosis/Diabetes mellitus ketoacidosis	87	96
	sepsis	–	74
	Multiple organ dysfunction syndrome	–	176
	Abdominal hypertension	–	45
	Abdominal compartment syndrome	–	35
	Acute peripancreatic fluid accumulation	–	164
	Acute necrotic accumulation	–	54
	Pseudocyst of pancreas	–	22
	Walled-off necrosis	–	20
Prognostic indicator			
	Intensive Care Unit Stay	–	98
	Mechanical Ventilation Days	–	17
	Continuous Renal Replacement Therapy	–	56

2. Methods

2.1. Definition

AP diagnosis requires two of the following three features [11]: (1) abdominal pain consistent with AP (acute onset of a persistent, severe, epigastric pain often radiating to the back); (2) serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; (3) characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT) and less commonly magnetic resonance imaging (MRI) or transabdominal ultrasonography.

MAP patients met the criteria of the Revised Atlanta Classification (RAC) [1]; non-MAP patients met the criteria of MSAP and SAP of RAC.

2.2. Data sources and study population

The laboratory data collected from 1533 patients diagnosed with AP at Zhongshan Hospital, Xiamen University, between August 2018 and August 2022 were retrospectively analyzed. The inclusion criteria was the first occurrence of AP. The exclusion criteria were: (1) age <18 years and >80 years; (2) non-first attack or an acute attack of chronic pancreatitis; (3) discharged within 7 days; (4) accompanied by hematologic disorders and solid tumors, chronic respiratory failure, chronic renal failure, autoimmune disorder; (5) incomplete clinical information.

A total of 623 AP, 402 males and 221 females, were included in the study (Table 1). The study was approved by the Ethics Committee of Zhongshan Hospital, Xiamen University. The study flow chart is shown in Fig. 1.

All routine clinical chemistry analyses such as renal & liver functions, serum electrolytes, and complete blood count were done as part of routine baseline assessment. Blood markers such as WBC count, IG%, and HFLC% were performed by Sysmex XN Series Hematology Analyzers. C-reactive protein (CRP), serum amylase (AMY), and lipase (LPS) were detected by Beckman AU5800 Full-automatic biochemical analyzer.

The study subjects were divided into two groups based on their clinical features, i.e., MAP (N = 358) and Non-MAP (N = 265). We divided patients in the Non-MAP group with complete data(101 patients) into HFLC% ≥ 2.9 %(31 patients) and HFLC% < 2.9 %(70 patients) according to the threshold of 7th day HFLC%. To estimate HFLC% at 7th day predictive value in Non-MAP regardless of the time of onset to hospital admission, we observed the prognostic indicators (ICU stay, complication, MV days and CRRT et al.) (Fig. 1)

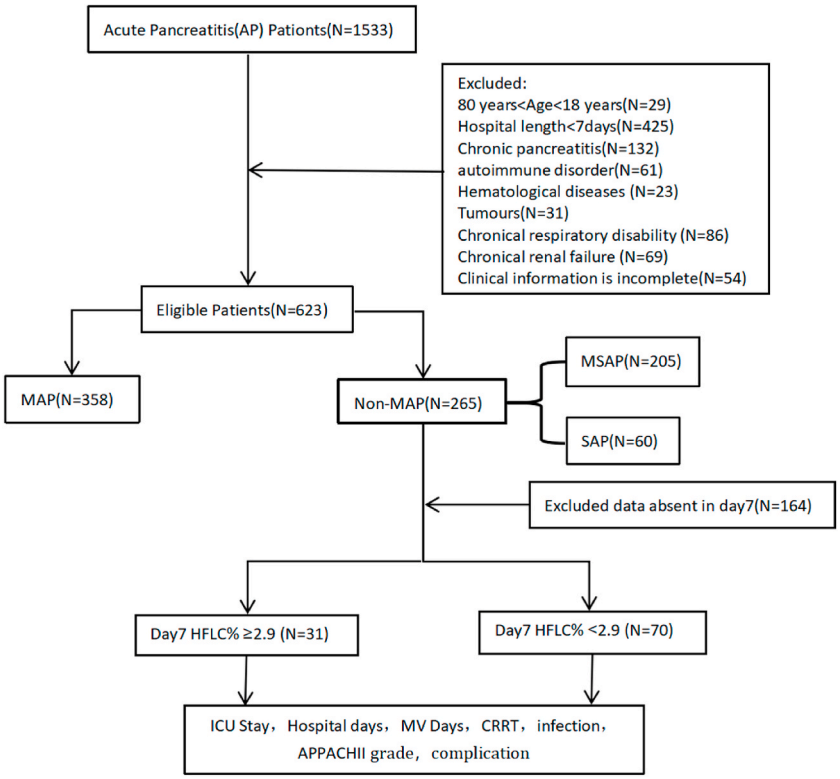

Fig. 1. The study flow chart.

2.3. Statistical analysis

Statistical comparisons were performed using the IBM SPSS Statistics 25.0 software package (IBM Corporation, USA). Descriptive statistics were expressed as unit number (N), percentage (%), and median/range (*M, IQR*). Comparison between the two groups was performed with the *Mann-Whitney U* test in the non-parametric rank sum test. Receiver operator characteristic curve (ROC) was performed to determine the diagnostic utility of various cut-offs of WBC, HFLC%, CRP, IG% and combined indicators. *Delong test* was used to compare the area under ROC curve of each experimental index on 7th day. The Youden index was used to detect the threshold level. *Pearson test* was used to detect correlations between variables. Association with AP complications and prognosis grouped by the decision threshold of HFLC% was analyzed by χ^2 test. $P < 0.05$ indicated statistical significance.

3. Results

The study cohort was classified into two groups as defined in the methodology. Group I, MAP (n = 358) and group II, Non-MAP (n = 265), cases (n = 265). Case files were assessed to exclude patients with date absent in 7th day(164 patients). Out of 101 patients, 31 had HFLC% ≥ 2.9 % by day 7 and 70 had HFLC% < 2.9 % by day 7.

MAP group (male 233, female 125) and Non-MAP group (male 169, female 96) showed no significant difference in gender and age (P_{gender}: 0.736; P_{age}: 0.062). In terms of etiology, there were 152 cases of biliary in origin, 202 cases with hyperlipidemia, and 4 cases of idiopathic disease in the MAP group. In the Non-MAP group, there were 113 cases with a biliogenic disease, 125 cases with hyperlipidemia, 15 cases with an alcoholic disease, and 6 cases of idiopathic disease (Table 1). WBC, IG%, and CRP were significantly higher in the Non-MAP group vs. MAP group (all $P < 0.05$), while the difference in HFLC% was not statistically significant ($P > 0.05$) (Table 2).

Continuous monitoring of blood indexes of AP patients after admission showed that WBC, IG% and CRP of AP patients in the Non-MAP group were higher than those in the MAP group during the 1st −12th day (all $P < 0.05$). On the contrary, from the 5th to 9th day, HFLC% in the MAP group was higher than that in the Non-MAP group; yet, the difference was statistically significant ($P < 0.05$) only on day 6 and 7 (Fig. 2).

Next, ROC curves were plotted for WBC, HFLC%, IG% and CRP on 7th day to assess the effectiveness of each blood index in predicting disease progression (Fig. 3). WBC, HFLC%, IG%, and CRP were all effective in predicting the progression of MAP to Non-MAP (all $P < 0.001$). Although the area under the ROC curve of HFLC% on the 7th day was larger than the other three indicators, the difference was not statistically significant($P > 0.05$). Combined with HFLC%, IG%,CRP and WBC, the ROC analysis showed that under ROC curve of the combined indicators was the largest ($AUC = 0.913$, $P < 0.001$) and had higher sensitivity and specificity than HFLC% ($P < 0.05$)(Tables 3 and 4).

In addition, we analyzed the *Youden* index of WBC, HFLC%, IG% and CRP to obtain the corresponding critical value (Table 3). HFLC % < 2.9 %, IG% > 1.7 %, CRP >28.66 mg/L, WBC >9.24 × 10^9/L indicates the possibility of aggravation of AP disease and should be executive intervention treatment earlier in clinical practice..

4. Discussion

Acute pancreatitis is a common disease with or without organ dysfunction. A pro-/anti-inflammatory imbalance is considered the key regulation of disease severity [12]. Various parameters are used to determine the clinical progression of pancreatitis. The immune system has an important role in acute pancreatitis progression [13]. Immature granulocytes (IGs) are pre-neutrophils of the maturation period from progenitor cells in the bone marrow. They belong to myeloid-derived suppressor cells (MDSCs), which are heterogeneous cells of myeloid origin, comprising myeloid progenitor cells and immature macrophages, immature granulocytes, and immature dendritic cells [14]. IGs, including promyelocytes, myelocytes and metamyelocytes, are usually not released or detected in peripheral blood in healthy individuals [15]. Karakulak et al. [16] reported that higher IG% levels correlate with higher disease severity and in-hospital mortality in patients with acute pancreatitis. Huang and colleagues [15] reported that IG% is a new biomarker for AP with ARDS, an efficient risk identification for early AP. Our study showed that IG% was significantly higher in those diagnosed with

Table 2
Comparative statistics of blood indexes between MAP and Non-MAP groups at initial diagnosis.

	MAP*(M,IQR)*	Non-MAP *(M, IQR)*	*Z*	*P*
	N = 358	N = 265		
Gender (%)	M 58.0 %; F 42.0 %	M 56.6 %; F 43.4 %	−0.338	0.736
Age (year)	47,18	48,23	−1.866	0.062
WBC (× 10^9/L)	11.10, 5.34	13.37, 6.19	−5.885	<0.001
HFLC (%)	0.0, 0.1	0.0, 0.1	−0.226	0.821
IG (%)	0.4, 0.3	0.5, 0.4	−4.022	<0.001
AMY (U/L)	377.4, 850.6	497.4, 1276.9	−1.724	0.085
LPS (U/L)	857.0, 2268.1	872.3, 2758.2	−1.027	0.305
CRP (mg/L)	11.11, 50.23	40.89, 162.70	−5.847	<0.001

WBC White blood cells, HFLC% Hyperfluorescent lymphocyte percentage, IG% Immature granulocyte percentage, AMY Amylase, LPS Lipase, CRP C-reactive protein.

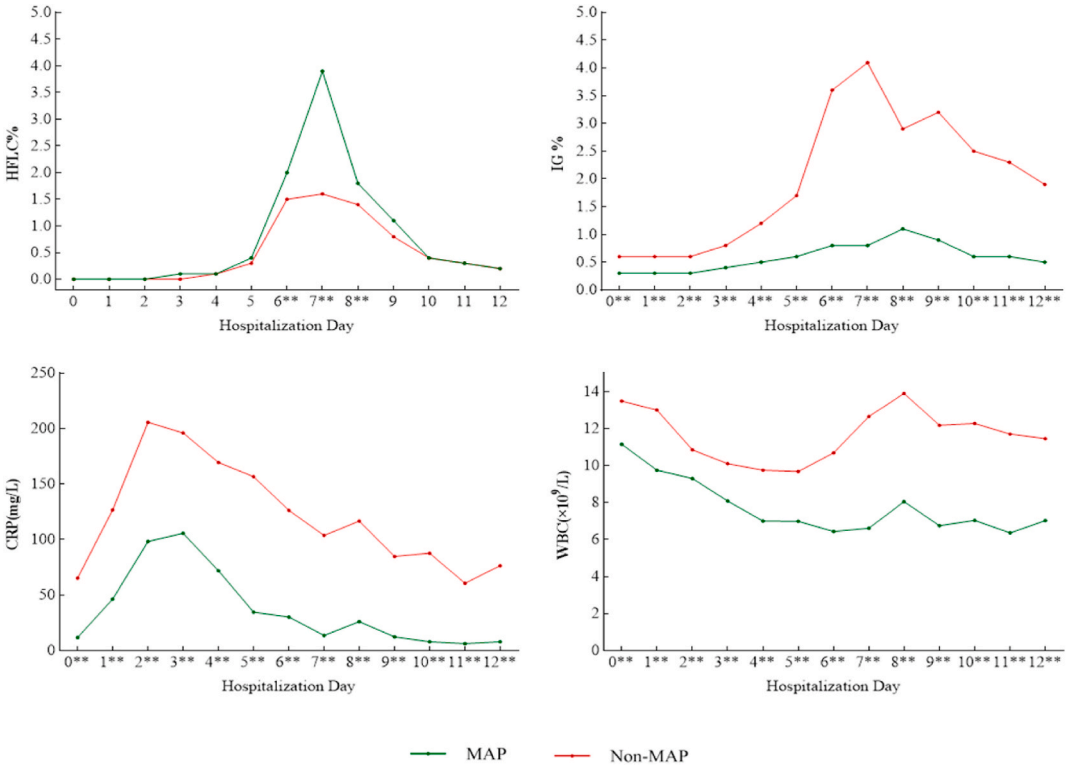

Fig. 2. Change curves of WBC, HFLC%, IG% and CRP of AP patients. The four line charts illustrate the change of HFLC%, IG%, CRP and WBC, comparing the MAP and Non-MAP groups. *$P < 0.05$, **$P < 0.01$.

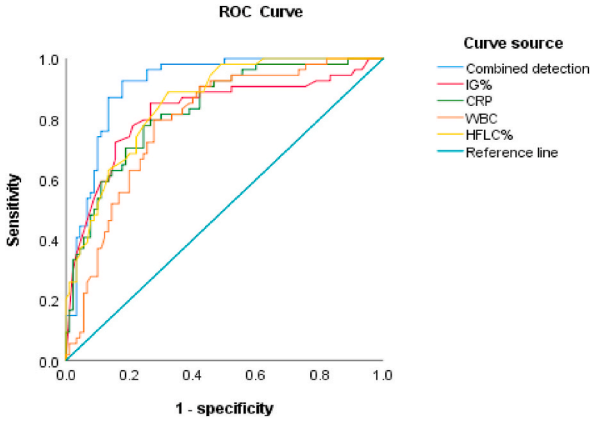

Fig. 3. ROC of WBC, HFLC%, IG%, and CRP in AP disease progression prediction on day 7.

Table 3
Effectiveness of WBC, HFLC%, IG% and CRP in predicting disease progression of AP in day7.

Project	*AUC*(95 % confidence interval)	*P*	*Youden*	Critical value
HFLC%	0.855 (0.795–0.914)	<0.001	0.589	2.9
IG%	0.824 (0.747–0.900)	<0.001	0.585	1.7
CRP(mg/L)	0.833 (0.766–0.899)	<0.001	0.534	28.66
WBC($\times 10^9$/L)	0.790 (0.716–0.865)	<0.001	0.518	9.24
Combined indicators	0.913 (0.867–0.960)	<0.001	–	–

HFLC% Hyperfluorescent lymphocyte percentage, IG% Immature granulocyte percentage, CRP C-reactive protein, WBC White blood cells. Combined indicators Combine detection of HFLC%,IG%,CRP and WBC.

Table 4
Comparison of pairwise sample region differences under ROC curve.

Compare items pairwise	*Z*	*P*	*AUC* discrepancy(95 % confidence interval)
IG% - HFLC%	−0.579	0.563	−0.031 (−0.136–0.074)
CRP - HFLC%	−0.490	0.624	−0.022 (−0.110–0.066)
WBC - HFLC%	−1.405	0.160	−0.064 (−0.154–0.025)
Combined indicators - HFLC%	−2.631	0.009	−0.059 (−0.103 ~ −0.015)

HFLC% Hyperfluorescent lymphocyte percentage, IG% Immature granulocyte percentage, CRP C-reactive protein, WBC White blood cells. Combined indicators Combine detection of HFLC%,IG%,CRP and WBC.

Next, we grouped the cut-off value of HFLC% and analyzed the difference between each complication and prognosis index between HFLC% ≥ 2.9 % and HFLC% < 2.9 %. There was no significant difference in gender and age between the two groups (P'_{gender}: 0.105; P'_{age}: 0.880). As shown in Table 5, HFLC% < 2.9 % was directly associated with infection, SIRS, and ICU admission (all $P < 0.05$). Further, there was a significant difference in ICU Days and APACHE-II score between groups ($P < 0.05$) and significant negative correlation between the HFLC% on 7th day and APPACHII score ($r_s = -0.312$, $P = 0.023$). HFLC% < 2.9 % on 7th day was indicated a larger proportion of infection, SIRS, more ICU days, and a higher APACHE-II score.

Table 5
χ^2 test for AP prognosis and complication indicators as assessed by the HFLC% threshold group on day 7.

Evaluation indicators	$HFLC\%_{Day7} \geq 2.9$ % (N = 31)	$HFLC\%_{Day7} < 2.9$ % (N = 70)	χ^2/Z	*P*
Gender(%)	M 54.3 %, F 45.7 %	M 51.6 %, F 48.4 %	−1.623	0.105
Age(year) (*M, IQR*)	48,16	45,21	−0.151	0.880
ICU Day (day) (*M, IQR*)	0,4	2,8	−2.293	0.022
Hospital Day (day)(*M, IQR*)	13,7	14,11	−1.361	0.173
APACHE-II score (*M, IQR*)	0.0,9.0	7.5,13.0	−2.221	0.026
Complication				
SIRS (%)	61.3	82.9	5.516	0.019
Septicemia (%)	29	41.4	1.407	0.236
MODS (%)	77.4	77.1	0.001	0.976
Celiac high pressure (%)	19.4	37.1	3.141	0.076
ACS (%)	9.7	30	4.898	0.027
Acute peripancreatic fluid collection (%)	64.5	64.3	0.000	0.982
ANC (%)	16.1	27.1	1.439	0.230
PP (%)	6.5	11.4	0.597	0.440
WON (%)	3.2	14.3	2.708	0.100
Infection (%)	35.5	64.3	7.215	0.007
Dropsy of serous cavity (%)	83.9	88.6	0.423	0.515
Prognosis				
CRRT (%)	25.8	38.6	1.546	0.214
MV Days (%)	6.5	14.3	1.259	0.262
ICU (%)	35.5	55.7	6.133	0.013

SIRS Systemic inflammatory response syndrome, MODS Multiple organ dysfunction syndrome, ACS Abdominal compartment syndrome, ANC Acute necrotic accumulation, PP Pseudocyst of pancreas, WON Walled-off necrosis, CRRT Continuous Renal Replacement Therapy, MV Mechanical Ventilation, ICU Intensive care unit.

Non-MAP than those with MAP. Yet, compared with CRP and WBC, IG% had no higher value in predicting early progression of AP, which is different from previus studies [9,17]. This suggested that the specificity and sensitivity of IG% are superior to CRP, which might be related to the time of the patient's initial visit.

By monitoring the IG% in AP patients from admission to the 14th day, we found that IG% increased more significantly in Non-MAP than in MAP patients. The proportion of MDSCs from the peripheral blood mononuclear cells was increased and positively correlated with AP severity [12], which also reflects the immune function status. These results suggested that the higher IG% indicates a more severe AP, which may be related to immunosuppression from the MDSCs.

HFLCs are activated lymphocytes with significantly increased nucleic acid substances by antigen stimulation, which morphologically look like atypical lymphocytes. The levels of histamine, bradykinin and cytokines cause inhibition of the immune system in the progress of AP. With pancreatic tissue self-digestion, the immune system causes a systemic immune stress response similar to infection, leading to B cell proliferation and replication. B cells produce inflammatory mediators and inhibit T cells. As a result, HFLC% increases. Our study showed no significant difference in HFLC% between the MAP group and the Non-MAP group ($P = 0.821$) on 1st day. However, continuous monitoring of the HFLC% of AP patients on the 1st to 12th day after admission showed that from the 5th day to the 9th day, the HFLC% in the MAP group was higher than that in the Non-MAP group; yet, HFLC% was significantly different only on day 6 and 7 ($P < 0.05$).

T lymphocytes have a vital role in the adaptive immune systems of multicellular organisms. With the progression of pancreatitis, the local imbalance of T-cell subsets in inflammatory and tumor environments and circulation has been observed [18]. MDSCs are potent suppressors of various T-cell functions [14]. Lili et al. [12] found increased inhibitory function to $CD3^+$ T cell proliferation in MDSCs derived from SAP patients. Consistent results were reported by Batikan and his team [13], who proposed that a low $CD4^+$ T cell and $CD3^+$ T cell ratio are associated with severe biliary pancreatitis. All these data suggest that the change in HFLC% in AP patients is

related to MDSC. HFLC% reflects lymphocytes activated by antigen stimulation in peripheral blood, including activated B cells, T lymphocytes, plasma cells and lymphocytes with high RNA content. As opposed to IG%, CRP, and WBC, HFLC% can reflect inflammatory stress and cellular immune function. Our study found that lymphocyte activation was significantly induced in the MAP group, and HFLC% increased at day 5–9, whereas the Non-MAP group showed a weaker activation, with a slight increase in HFLC%. The results indicated that rather MSAP or SAP could not fully mobilize the normal immune defense response. Compared with the MAP group, Non-MAP showed more serious immune dysfunction, which was related to complications and mortality in severe AP patients. Qin et al. [19] proposed uncontrolled inflammatory response in the early stage and immune dysfunction in the late stage in SAP patients, showing reduced lymphocytes, decreased proliferation, and unresponsiveness to antigenic stimulation.

By analyzing the 7th day ROC curve of HFLC%, IG%, CRP and WBC of AP patients, we found that though the area under ROC curve of HFLC% was larger than IG%, CRP and WBC, but it was not statistically significant compared with the other three comparisons ($P > 0.05$). In addition, a threshold of HFLC% (2.9 %) was then obtained by the Youden index, and cases were divided into two groups, i.e., HFLC% $\geq$ 2.9 % and HFLC% $<$ 2.9 %. We analyzed the difference between complication and prognosis, and reached the conclusion that HFLC% $<$ 2.9 % might indicate a larger proportion of infection, SIRS, longer ICU days, and a higher APACHE-II score (Table 5). While HFLC% $<$ 2.9 % may suggest that patients have more seriously impaired immune function and severity of illness. As well as known that APACHE-II consists of acute physiological parameters (APS), chronic health status (CHS) and age. It can make a quantitative evaluation of a patient's condition [20]. The higher the score, the more serious the condition, the worse the prognosis and the higher the fatality rate. But the APACHE-II score still has limitations about whether patients truthfully state their past history and clinicians' subjective judgment. Our findings suggested that there was a significant negative correlation between the HFLC% on 7th day and APPACHII score ($r_s = -0.312$, $P = 0.023$). So HFLC% may be an independent laboratory marker for prognosis in AP and it would be a good indicator to monitor the immune function and evaluate inflammatory situations in admitted AP patients. Futher, HFLC% is an objective laboratory index, which can effectively avoid the shortcomings of the subjective judgment existing in the APACHE-II score. Analysis of the HFLC% together with IG%, CRP and WBC helps evaluate AP patients' immune situation and prognosis.

The present study has a few limitations. This is a retrospective analysis with a relatively small sample size, so the results may lack robustness. In the future, we will continue to collect SAP cases and increase the number of SAP cases before making analyses and statistics. The relationship between MDSCs and the body's immune function and its changes and mechanisms in severe clinical cases such as SAP is our new research direction.

5. Conclusion

The study shows that HFLC% is not an early diagnosis predictor of MSAP or SAP, but a reliable indicator for monitoring the immune function and a potential independent laboratory marker for infection and prognosis in AP. HFLC% $<$ 2.9 % on day7 post-admission was related to more infection, SIRS, ICU days, and a higher APACHE-II score. When HFLC% was $<$2.9 %, the patients had more seriously impaired immune function and state of illness. HFLC% has the potential to become a useful laboratory marker for assessing prognosis of AP. The method is simple and easily standardized, and suitable for clinical use. Combining HFLC% with IG%, CRP and WBC will be more helpful in evaluating AP patients' disease development and outcome.

Ethics statement

The subjects included in this study were adults, and all of the subjects provided written informed consent in accordance with the institutional guidelines prior to the study. This study was approved by the Institutional Ethics Committee of Zhongshan Hospital, School of Medicine, Xiamen University, and complied with national legislations and the Declaration of Helsinki guidelines (xmzsyyky-2023-063).

Data Availability statement

We declare that data related to our research are not publicly available at this time for the following reasons: ① The preliminary statistical results have been reflected in our paper; ② The experimental data is related to our subsequent research, and research data will not be disclosed until the later research results are published.

CRediT authorship contribution statement

Lin Xiao-yan: Writing – review & editing, Writing – original draft, Validation, Methodology. **Li Xiao-ling:** Investigation, Data curation. **Zhang Le-xin:** Investigation, Data curation. **Sheng Nan:** Data curation. **Chen Yu:** Visualization, Data curation. **Liu Hui-heng:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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