Japanese Journal of Gastroenterology and Hepatology

Review Article

Association of high Altitude Polycythemia with an Increased Risk of Systemic Inflammatory Response Syndrome in Acute Pancreatitis

Zhu H[1*], Guo YM[1], Yang JY[1], Yexie ZH[1], Bai YL[1] and Cao T[1, 2]

[1]Department of General Surgery, Qinghai Provincial People's Hospital General Surgery, Xining, Qinghai, China

[2]Department of Gastroenterology, Qinghai University Medical College, China

Received: 05 Mar 2020

Accepted: 28 Mar 2020

Published: 31 Mar 2020

[*]Corresponding author:

Hai-Hong Zhu, Department of General Surgery, Qinghai Provincial People's Hospital, Xining 810007, Qinghai, China, E-mail: zhuhaihong1214@126.com

1. Abstract

1.1. Objective: To investigate the relationship between systemic inflammatory response syndrome (SIRS) and the severity of acute pancreatitis with high altitude polycythemia (hereinafter referred to as AP+HAPC) in individuals living in a high-altitude region, to provide evidence for the treatment of SIRS and AP+HAPC.

1.2. Methods: A retrospective analysis of clinical data on AP+HAPC and acute pancreatitis without high altitude polycythemia (hereinafter referred to as AP-only) was conducted in100 in patients admitted to the People's Hospital of Qinghai Province from 2006 to 2016. All 100 cases were evenly categorized into 2 groups according to diagnostic criteria: AP+HAPC group (n=50) and AP-only group (n=50). The patients in the high altitude polycythemia group were further divided into mild and severe subgroups based on the Acute Physiology and Chronic Health Evaluation II scores. The data were analyzed based on the presence of SIRS, number of diagnostic criteria met, diagnostic parameters, and relationship between severity of AP+HAPC and duration of SIRS.

1.3. Results: There was a significant difference between the 2 groups (AP+HAPC vs. AP-only) not only in the number of patients who developed SIRS but also in 2 diagnostic criteria of SIRS fulfilled by patients. There was a significant statistical difference in terms of 5 diagnostic parameters of SIRS between the high altitude polycythemia group and the non-high altitude polycythemia group. The significant differences between 2 and 3 diagnostic criteria of SIRS fulfilled by patients were found to be related to the severity of SIRS in patients with AP+HAPC; the greater the severity of AP+HAPC, the longer the duration of SIRS.

1.4. Conclusions: SIRS is highly correlated with the severity of AP+HAPC in individuals living in a high-altitude region. Early and active treatment of SIRS is beneficial in the management of AP+HAPC.

2. Keywords: Systemic inflammatory response syndrome; Acute pancreatitis; High altitude polycythemia

3. Introduction

High altitude polycythemia, a clinical syndrome that occurs to residents living above 2500 meters, is characterized by redundant erythrocytosis and serious hypoxemia [1]. Case-control studies suggest that baseline hypoxemia can serve as a promising prognostic indicator in patients with acute pancreatitis, especially in patients with early severe acute pancreatitis [2-3]. Furthermore, decreased Oxygen delivery to the organ contributes to injury [4]. Acinar cell injury re-

sults in a limited inflammatory reaction, which may develop into a systemic inflammatory response syndrome if it is uncontrolled [5]. It is reported that the severity of acute pancreatitis is greater among patients with SIRS on day 1 and, in particular, among those with 3 or 4 SIRS criteria, compared with those without SIRS on day 1 [6].

However, to our knowledge, there has been no case-control studies of the relationship between systemic inflammatory response syndrome and severity of acute pancreatitis combined with high altitude polycythemia. Identifying the risk of SIRS involved in acute pancreatitis patients with high altitude polycythemia would allow clinicians pay more attention to this special population and provide more timely treatment for patients.

We therefore hypothesized that acute pancreatitis patients with high altitude polycythemia possess more severe SIRS and adverse outcomes compared with acute pancreatitis patients without high altitude polycythemia. To test this hypothesis, we undertook a case-control study to compare the number of SIRS and outcome between two groups.

4. Data and Methods

4.1. Data source

This was a case-control study on the basis of the database of the People's Hospital of Qinghai Province. This study was approved by the Ethics Review Board of the People's Hospital of Qinghai Province.

4.2. Identification of Cases and Controls

We collected the clinical data of 50 acute pancreatitis patients combined with high altitude polycythemia in the People's Hospital of Qinghai Province during the period of 2006-2016. To reduce biased results, subjects undergoing a medical history of any heart, lung, liver, or kidney disease, as well as diabetes, autoimmune diseases and cancer, were excluded from the study. The case group comprised 28 men and 22 women, with a mean age of 48±5 years (range, 45-59 years). All cases were admitted to the hospital within 24 h after the symptoms first appeared. Further, the control group comprising 50 patients with AP but without HAPC (hereinafter referred to as AP-only) was randomly selected according to the same criteria, which consisted of 31 men and 19 women. The clinical materials of two groups were collected and evaluated according to the Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, in which ≥8 point indicates severe disease. Thereafter, the patients in the AP+HAPC group were subdivided into mild and severe subgroups.

4.3. Diagnostic Criteria

4.3.1. Diagnostic criteria of SIRS: According to the definition and diagnostic criteria of SIRS specified by the ACCP/SCCM in August 1991 [7], SIRS is an inflammatory state affecting the whole body and is often a response to a variety of severe injuries. These injuries can either be infectious or non-infectious, including severe trauma, burns, and pancreatitis.

The presence of SIRS was confirmed if ≥2 of the following criteria were met:

- Temperature >38°C or <36°C;
- Heart rate >90 beats/min;
- Respiratory rate >20 breaths/min, or arterial carbon dioxide partial pressure ($PaCO_2$) <32mmHg (4.3kPa);
- White blood cell count>12,000/mm^3 or <4000/mm^3,or immature cells >10%.

4.3.2. Diagnostic Criteria of AP: The diagnostic criteria of AP were based on the "Atlanta Classification and Definitions of AP" and the "AP Clinic Diagnostic Criteria" published by the Chinese Medical Association in 2012 [8-11].

4.3.3. Diagnostic Criteria of HAPC: The diagnostic criteria of HAPC included hemoglobin ≥200 g/L, red blood cell count ≥6.5×10^{12}/L, and hematocrit ≥65%. The clinical manifestations involved varying severities of high-altitude sickness, including headache, dizziness, cyanosis, and other plethoric symptoms [12-15].

4.3.4. Classification Reference and Evaluation Methodology: According to the APACHE-II scores for classifying the severity of AP, a score of ≥8 points means severe AP and a score of <8 means mild AP.

4.3.5. Research index: The evaluated parameters included sex, age, medical history, years of residency in Qinghai, place of residence, blood pressure, pulse rate, respiratory rate, blood gas, blood routine examination, and duration of SIRS, number of fulfilled diagnostic criteria of SIRS, hospital admission duration, and length of hospital stay.

4.3.6. Methods: We analyzed the clinical data of the 50 AP+HAPC cases and the 50AP-only cases randomly selected from our hospital. We performed a comparative analysis on whether the patients have SIRS, the number of diagnostic criteria met, the diagnostic index of SIRS, and the relationship between the severity of AP+HAPC and the duration SIRS.

4.3.7: Statistical analysis

All measured values are presented as average value ± standard deviation ($\bar{x} \pm SD$), and the test of significance was conducted on 2 sample means for the count and measurement data, specifically by using the χ^2, t, and rank-sum tests. For correlations of categorical data, association analysis was adopted and data were presented as contingency coefficients, Statistical analysis was done using SPSS22.0 software, and the probability value <0.05 was considered statistically significant.

5. Results

5.1. Characteristics of the study population

There were 50 subjects in the case group and 50 subjects in the control group, with similar distributions of sex and age. Among the 50 AP+HAPC cases, 50 patients had sudden upper abdominal pain (100%), 50 patients had nausea and vomiting (100%), and 38 patients had increased white blood cell count (76%). Further, 50 patients had increased urine amylase (100%); the blood amylase level was 624.12±104.00IU/L, whereas the urine amylase level was 1412.58±189.10 IU/L. Moreover, 48 patients had increased lipase level (457.22±61.44 U/L), 18 patients had combined cholelithiasis (36%), 18 patients had cholecystitis (36%), and 18 patients had decreased blood pressure (<12/8 kPa)(90%).

5.2. Treatment and Outcomes

All cases were fasting, established the vein passage, received anti-inflammatory treatment, had good suppression of pancreatic secretion, underwent spasmolysis, had decreased pancreatic enzymatic activity, and avoided taking medications with renal toxicity. Surgery was needed to remove necrotic pancreatic tissue in 2 cases. Of all the 50 patients,2 patients died of shock and 3 died of multiple organ failure.

5.3. Comparisons between Patients of the HAPC and Non-HAPC Groups

There was a significant difference (*P*<0.05, see (Table 1)) between the HAPC and non-HAPC groups in terms of whether the patients had SIRS and the number of diagnostic criteria met.

Table 1: Comparisons between the AP+HAPC group and AP-only groups, cases (%).

Group	Non-SIRS	SIRS	2 Criteria met	3Criteria met	4 Criteria met	Total
Plateau erythrocythemia	6/50 (12.0)	44/50 (88.0)	25/44 (56.8)	14/44 (31.8)	5/44 (11.1)	50
Non-plateau erythrocythemia	32/50 (64.0)	18/50 (36.0)	4/18 (22.2)	10/18 (55.6)	4/18 (22.2)	50
χ^2	28.693		6.141	3.034	0.496	
P	<0.001		0.013	0.082	0.481	
Total	38/100 (38.0)	62/100 (62.0)	29/62 (46.8)	24/62 (38.7)	9/62 (14.5)	100
SIRS, systemic inflammatory response syndrome.						

5.4. Comparisons of the Diagnostic Criteria of SIRS between the HAPC and Non- HAPC Groups

There was a significant difference (*P*<0.05, see (Table2)) between the 2 groups in terms of 5 specific diagnostic parameters.

Table 2: Comparisons of SIRS diagnostic parameters between the plateau erythrocythemia and non-plateau erythrocythemia groups, (x) ±s

Group	Temperature (°C)	Heart rate (beats/min)	Respiratory rate (breaths/min)	$PaCO_2$ (mmHg)	WBC (×10⁹/L)
Plateau erythrocythemia	37.88±0.62	112.26±15.24	23.08 ±4.02	37.58±3.12	12.89±5.12
Non-plateau erythrocythemia	37.42±0.74	90.04±20.35	19.07±2.01	30.25±3.43	10.65±4.51
T value	3.37	6.18	6.31	11.18	2.32
P value	0.001	<0.001	<0.001	<0.001	0.022
SIRS, systemic inflammatory response syndrome; PaCO2, arterial carbon dioxide partial pressure; WBC, white blood cell.					

5.5. Comparisons of the Relationship between the AP+PE Mild and Severe Subgroups in 44 Cases

There was a significant difference(*C*=0.569, *P*<0.05; see (Table3)) between the AP+PE mild and severe subgroups in terms of 2 and 3 diagnostic criteria of SIRS.

Table 3: Comparison of the relationship between the severity of AP+PE combined with SIRS and SIRS in 44 cases

Group	No. of cases	2 Criteria met	3 Criteria met	4 Criteria met
Mild	30	24 (80.0)	5 (16.7)	1 (3.3)
Severe	14	1 (7.10)	9	4 (28.6)
			-64.3	
C			0.569	
P			<0.001	
SIRS, systemic inflammatory response syndrome; AP+PE, acute pancreatitis with plateau erythrocythemia. C,coefficient of contingency				

5.6. Relationship between the Severity of AP+HAPC and the Duration of SIRS

(Table4) presents that the greater the severity of AP+HAPC is proportional to the duration of SIRS (Z=-4.408, *P*<0.001).

Table 4: Relationship between the severity of AP+PE and the duration of SIRS

Group	No. of cases	Non-SIRS	SIRS lasting 1 d	SIRS lasting 2 d	SIRS lasting 3 d	SIRS lasting 4 d	SIRS lasting 5 d	SIRS lasting 6 d	SIRS lasting 7 d
Mild	36	6	4	6	9	6	3	1	1
Severe	14	0	0	0	1	2	3	4	4
SIRS, systemic inflammatory response syndrome; AP+HAPC, acutepancreatitis with plateau erythrocythemia.									

6. Discussion

The statistical analysis of the number, severity and duration of SIRS in acute pancreatitis patients with high altitude polycythemia and the control group confirms a positive correlation between SIRS and acute pancreatitis patients with high altitude polycythemia. Indeed, the proportion of SISR in the case group is 88% while it is only 36% in the control group. In addition, the subgroup of severe cases satisfies more criteria and has a longer average duration than the subgroup of mild cases.

In recent years, it has been thought that hypoxemia is independently related to an increased risk of acute pancreatitis. One recent report showed that among 166 patients with acute pancreatitis, the odds ratio of hypoxemia to healthy patients with acute pancreatitis was 9.56 [2]. A basic science study found that acute hypoxemia result in activation of the neutronphil, which is an essential component in the systemic inflammatory response syndrome [16]. However, to date, it is a lack of convincing and direct evidence to reveal the relationship between systemic inflammatory response syndrome and severity of acute pancreatitis combined with high altitude polycythemia.

The current study clarifies these previous findings and extends them to a case-control study to be representative of patients seen in clinical practice. In our study, we first revealed the increased severity of SIRS in acute pancreatitis patients combined with high altitude polycythemia. Because of the sample size of the study, we were capable of inspecting carefully the prognostic significance of high altitude polycythemia. Besides, the cases group was divided into two subgroups to explore the association between SIRS and acute pancreatitis on the basis of APACHE-II scores. At last, our results keep consistent with our previous hypothesis that acute pancreatitis patients with high altitude polycythemia have more severe SIRS and adverse outcomes compared with acute pancreatitis patients without high altitude polycythemia.

There are some shortcomings inherent to this study. First, our study is a case-control study, which is less convincing than the cohort study. Thus, the result of the study should be interpreted with caution. More clinical trials, especially the long-term cohort study are needed to give more information. Second, the enrolled population was a heterogeneous one, including patients who underwent test in various physiological or pathological states. Considering the above situation, we adopted an independent method of examining the basic situation of subjects, and excluded the subjects undergoing a medical history of any heart, lung, liver, or kidney disease, as well as diabetes, autoimmune diseases and cancer from the study.

The finding of a positive correlation between SIRS and acute pancreatitis patients with high altitude polycythemia is important for clinical practice. Our results showed that there was a significant difference between the HAPC group and the non-HAPC group in two diagnostic criteria of SIRS fulfilled by patients. There was a significant statistical difference in three diagnostic parameters of SIRS between the two groups. The significant differences in two and three diagnostic parameters of SIRS fulfilled by patients were found to be related to the severity of SIRS among patients with AP+HAPC; the greater the severity of AP+HAPC, the longer the duration of SIRS.

From this research, with respect to the diagnostic parameters of SIRS, differences in pulmonary function were found between the AP+HAPC and AP-only groups. The respiratory rate and the $PaCO_2$ of the AP+PHAPC group were both higher than those of the AP-only group. Specifically, the respiratory rates were 23.08±4.02 breaths/min vs. 19.07±2.01 breaths/min, and the $PaCO_2$ values were 37.58±3.12 mmHg vs. 30.25±3.43 mmHg. Patients with AP+HAPC are more likely to have decreased pulmonary function with the progression of the disease, and also have a higher possibility of developing SIRS.

We believe that AP and HAPC have a synergistic pathogenesis that causes a systemic inflammation reaction chain, leading to a severe SIRS response. Hence, for patients with HAPC, besides the necessary pharmaceutical management, the "deep breathing method" should also be employed to increase pulmonary ventilation and thereby accelerate the recovery process.

Lastly, the development of SIRS and the severity of AP+HAPC are closely related. Patients with HAPC are more vulnerable to the effects of AP with concomitant SIRS. In conclusion, the key to treating AP+HAPC is the prevention and management of SIRS. In addition, treating HAPC itself must not be neglected.

References

1. Leon-Velarde F, Maggiorini M, Reeves JT, Aldashev A, Asmus I, Bernardi L et al. Consensus statement on chronic and sub acute high altitude diseases. High Alt Med Biol 2005; 6: 147-57.

2. Polyzogopoulou E, Bikas C, Danikas D, Koutras A, Kalfarentzos F, Gogos CA et al. Baseline hypoxemia as a prognostic marker for pulmonary complications and outcome in patients with acute pancreatitis. Dig Dis Sci. 2004; 49: 150-4.

3. Tao HQ, Zhang JX, Zou SC et al. Clinical characteristics and management of patients with early acute severe pancreatitis: Experience from a medical center in China.World J Gastroenterol. 2004; 10: 919-21.

4. Frossard JL, Steer ML, Pastor CM et al. Acute pancreatitis. Lancet 2008; 371: 143-52.

5. Bhatia M. Inflammatory response on the pancreatic acinar cell injury. Scand J Surg. 2005; 94: 97-102.

6. Singh VK, Wu BU, Bollen TL, Repas K, Maurer R, Mortele KJ, Banks PA et al. Early systemic inflammatory response syndrome is associated with severe acute pancreatitis. Clin Gastroenterol Hepatol. 2009; 7: 1247-51.

7. American College of Chest Physicians/Society of Critical Care

Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992; 20: 864-74.

8. Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. Arch Surg. 1993; 128: 586-90.

9. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG et al. Acute Pancreatitis Classification Working Group.Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013; 62: 102-11.

10. Nawaz H, Mounzer R, Yadav D, Yabes JG, Slivka A, Whitcomb DC, Papachristou GI. et al. Revised Atlanta and determinant-based classification: application in a prospective cohort of acute pancreatitis patients. Am J Gastroenterol. 2013; 108: 1911-17.

11. Pancreas Study Group, C. S. o. G., Chinese Medical Association, Editorial Board of Chinese Journal of Pancreatology, Editorial Board of Chinese Journal of Digestion. Chinese guidelines for the management of acute pancreatitis (Shanghai, 2013). J Clin Hepatol. 2013; 29.

12. Jiang C, Chen J, Liu F, Luo Y, Xu G, Shen HY et al. Chronic mountain sickness in Chinese Han males who migrated to the Qinghai-Tibetan plateau: application and evaluation of diagnostic criteria for chronic mountain sickness. BMC Public Health. 2014; 14: 701.

13. Azad P, Zhao HW, Cabrales PJ, Ronen R, Zhou D, Poulsen O et al. Senp1 drives hypoxia-induced polycythemia via GATA1 and Bcl-xL in subjects with Monge's disease. J Exp Med. 2016; 213: 2729-44.

14. De Ferrari A, Miranda JJ, Gilman RH, Dávila-Román VG, León-Velarde F, Rivera-Ch M et al. clinical profile, iron status, and subject-specific traits for excessive erythrocytosis in andean adults living permanently at 3,825 meters above sea level. Chest. 2014; 146: 1327-36.

15. Villafuerte FC, Corante N et al. Chronic mountain sickness: clinical aspects, etiology, management, and treatment. High Alt Med Biol. 2016; 17: 61-9.

16. Tamura DY, Moore EE, Partrick DA, Johnson JL, Offner PJ, Silliman CC et al. Acute hypoxemia in humans enhances the neutrophil inflammatory response. Shock. 2002; 17: 269-73.