A new diagnostic strategy with neutrophil counts in patients with suspected aortic dissection in a certain time window

HON CHUN (ch093@ha.org.hk)
Tsueng Kwan O hospital
Kai Man SIU
United Christian Hospital, Hong Kong

Research Article

Keywords: Neutrophil, aortic dissection, aortic dissection detection

Posted Date: May 20th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1618397/v1

Abstract

Background: Neutrophil counts are increased in aortic dissection (AD) patients. However, the diagnostic value of neutrophil counts has not been validated.

Methods: Patients with suspected AD from two clinical centers were retrospectively enrolled from 01/07/2011 to 30/06/2021. Clinical characteristic data, including history, onset time, diagnosis, and neutrophil counts, were collected.

Results: A total of 198 of 534 (37.1%) patients were diagnosed with AD. The neutrophil counts were significantly higher in AD patients during the 2 to 24-hour interval after symptom onset. In this time window, increased neutrophil counts had a sensitivity of 95.6%, specificity of 56.1%, negative likelihood ratio of 0.08, and negative predictive value of 95.6%.

Conclusions: Neutrophil counts may be useful in risk stratification of patients to rule out aortic dissection if used within 2-24 hours after symptom onset.

Introduction

Aortic dissection (AD) is a potentially devastating cardiovascular disease worldwide. However, given the low incidence of AD (2.5 to 3.5 cases per 100,000 person-years), the diagnosis of this disease remains relatively difficult in acute settings [1, 2]. As a result, validated clinical strategies beyond clinical judgment are needed to manage patients with suspected AD.

The aortic dissection detection (ADD) risk score combined with the D-dimer level is currently widely used as a clinical tool to estimate the risk of AD [3-5]. However, the measurement of D-dimer levels requires a relatively time-consuming test that may not be available in every acute setting. Neutrophil counts are indicators of inflammation that have been used in the clinic for a long time, and it is easy to obtain these numbers quickly. Neutrophil counts (or neutrophil to lymphocyte ratios) were found to be increased in acute aortic dissection patients and to be related to disease prognosis [6-9]. However, those research articles only compared the white blood cell status between AD patients and normal patients (or chronic aortic aneurysm patients). This control group is not representative of high-risk patients in acute settings. As a result, the aim of our study was to confirm that neutrophil counts can be used a new diagnostic tool and to try to replace the use of D-dimer levels to some extent.

Methods

Patient selection and study population

This was a retrospective diagnostic accuracy study, and all suspected AD patients in the Kowloon East Hospital cluster, including United Christian Hospital and Tseung Kwan O Hospital, were included.

From 07/01/2011 to 30/06/2021, patients were included in the AD registry if they met all the following criteria, which were similar to those previously used in the IRAD-Bio study [10]: sufficiently high suspicion of AD to cause the evaluating physician to order computed tomography aortogram (CTA) to identify the presence or absence of AD. The exclusion criteria were as follows: (1) no neutrophil counts recorded before invasive treatments; (2) age <18 years old; (3) cardiac arrest occurred before blood tests; (4) recent history of major trauma; and (4) risk of neutropenia, including that due to chemotherapy, hematology disease, etc. The standard data entry form included information about patient demographics, history, onset time, presentation, physical findings, and imaging study results. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The District Ethics Boards approved the study (KC/KE-21-0222/ER-1).

Clinical risk score

The clinical information relevant to the ADD risk score was obtained from AED notes, admission notes, and investigation forms. The data not reported in the charts were assigned a negative result by default.

The conditions considered to predispose a patient to ADD were as follows: (1) history of Marfan syndrome or other connective tissue disease, (2) family history of aortic disease, (3) history of known aortic valve disease, (4) history of recent aortic manipulation, and (5) history of known thoracic aortic aneurysm.

The pain features associated with ADD were as follows: (6) abrupt pain onset, (7) severe pain intensity, and (8) pain similar to ripping or tearing. For charts that reported a pain scale, the severity of pain was defined with a numeric rating scale (NRS-11) of 7–10. For charts that did not report a pain scale, pain severity was defined based on the explicit definition of severity recorded on the chart by the attending physician or the administration of any opioid drug or ≥2 analgesic drugs.

The ADD physical findings were as follows: (9) pulse asymmetry or systolic blood pressure differential ≥20 mm Hg between extremities, (10) focal neurological deficit, (11) new murmur of aortic insufficiency, and (12) shock state or hypotension (systolic blood pressure ≤90 mm Hg).

The ADD risk score was calculated based on the number of categories where at least one risk marker was present[3]. As stated in the European Society of Cardiology (ESC) guidelines[5], patients were divided into low probability (ADD risk score≤1) and high probability (ADD risk score >1) groups.

Neutrophil counts

Neutrophil counts were measured with an automated hematology analyzer (XN-3000, Sysmex Corp., Hyogo, Japan), and the normal range was $1.5\sim6.2*10^9$/L. If patients were subjected to serial blood tests to measure neutrophil counts, the earliest neutrophil count was recorded.

Statistical analysis

Continuous variables are expressed as proportions, and continuous data are expressed as the mean and standard deviation (SD); categorical variables were compared using the two-sided chi-square test or, when appropriate, the two-sided Fisher's exact test. Comparison of normally distributed continuous variables between two groups was performed using the unpaired, two-sided Student's t test or paired sample t test (in paired samples).

The diagnostic value of neutrophil counts (cutoff value: $6.2*10^9$/L) was assessed by calculating the sensitivity, specificity, negative and positive predictive values (NPV and PPV) and negative and positive likelihood ratios (NLR and PLR) with their 95% confident interval (95% CI) for all patients.

p-values were two-sided, and a P value lower than 0.05 was considered statistically significant. Analyses were performed with the SPSS statistical package (version 24.0, SPSS Inc., Chicago, Illinois).

Results

Clinical characteristics of the study population

During the study period, 736 patients were evaluated for suspected AD, and 534 patients were enrolled in the study. Among the 534 patients (mean age 65.2±14.6 years, 69.2% males), 198 (37.1%) had a final diagnosis of AD; among these patients, 122 (61.6%) patients had type A AD, and 75 (37.8%) patients had type B AD.

Of the 336 (62.9%) patients in whom AD was ruled out, 105 (31.3%) had acute coronary syndrome, 2 (0.6%) had pulmonary embolism, 140 (41.7%) had atypical chest pain, and 89 (26.5%) had other diagnoses. The clinical characteristics, past medical histories and prevalence of ADD risk markers in patients in the AD group and control group are presented in Table 1.

Female sex, high heart rate, histories of diabetes, ischemic heart disease, and stroke were more frequently observed in the control group. Predisposing conditions and pain features were more often observed in patients with AD. However, pulse deficits were more frequently reported in the control group.

The distribution of time intervals between symptom onset and blood collection in these patients was also calculated and is shown in Table 2. A total of 32.3% of AD patients had blood drawn within 2 h of symptom onset, and a total of 77.7% of AD patients had blood drawn within 24 h. In contrast, 25.3% of non-AD patients had blood drawn within 2 h of symptom onset, and a total of 71.7% of AD patients had blood drawn within 24 h.

ADD risk score

The results of the ADD risk score are shown in Table 3. A low probability was observed in 65.6% of AD patients versus 75.0% of non-AD patients. In contrast, a high probability was more frequently observed in AD patients (34.3% vs. 25.0%, P=0.021).

Diagnostic performance of neutrophil counts

The sensitivity and specificity of neutrophil counts (cutoff: $6.2*10^9$/L) in the general study population were 69.2% (95% confidence interval (CI) 62.2-75.4) and 56.0% (95% CI 50.5-61.3), respectively. The negative and positive predictive values (NPV/PPV) of neutrophil counts for AD were 75.5% and 48.1%, respectively, while the negative and positive likelihood ratios (NLR/PLR) of neutrophil counts were 0.55 and 1.57, respectively.

Because of the low sensitivity for AD diagnosis, further data analysis according to time intervals was performed. Figure 1 shows increased neutrophil counts in both the 2-8 hour (h) time interval and the 8-24 h time interval (both P<0.001), and there were no statistically significant differences between AD and control patients in other time intervals.

The sensitivity and specificity in the 2-8 h interval were 94.8% (95% CI 84.7-98.6) and 59.4% (95% CI 50.0-68.4), respectively, and similar sensitivity and specificity were observed in the 8-24 h interval group (96.9% and 45.0%, respectively) (Table 4).

Diagnostic value of the ADD risk score with neutrophil count

We combined the 2-8 h and 8-24 h groups into a new group (the 2-24 h group), with a sensitivity of 95.6% (95% CI 88.4-98.6), a specificity of 56.1% (95% CI 47.9-63.9), a NPV of 98.6%, a NPV of 55.5%, a NLR of 0.08, and a PLR of 2.71. Further analysis of the ADD risk scores was carried out in patients with data in the a 2-24 h time interval (Table 5).

The sensitivity and specificity of high probability (ADD>1) in patients in the 2-24 h interval were relatively low, 34.3% (94% CI 27.8-41.5) and 75.0% (95% CI 69.9-79.5), respectively. The sensitivity and specificity of neutrophil counts in low-probability patients were 94.6% (95% CI 84.2-98.6) and 52.3% (95% CI 42.1-61.9), respectively.

According to the ADD risk score, patients with AD who had either a low probability score or a high probability score showed significantly increased neutrophil levels compared to non-AD patients in the same risk group (Figure 2a).

The diagnostic value of neutrophil counts alone and neutrophil counts combined with the ADD risk score is presented in Table 5. The area under the curve (AUC) of the ROC analysis was 0.82 (95% CI 0.76-0.87, P<0.001) for neutrophil counts in all the 2-24 h interval study groups (Figure 2b, cutoff level of $6.2*10^9$/L, with a sensitivity of 95.6% (95% CI 88.4-98.6), specificity of 56.1% (95% CI 47.9-63.9), NPV of 95.6% and failure rate of 4.3%). In the low probability group (Figure 2c), the AUC was 0.80 (95% CI 0.73-0.87, P<0.001, sensitivity of 94.6% (95% CI 84.2-98.6), specificity of 52.3% (95% CI 42.1-61.9), NPV of 95.0% and failure rate of 5.0%). In the high probability group (Figure 2d), the AUC was 0.84 (95% CI 0.77-0.92, p<0.001, sensitivity of 97.1% (95% CI 82.9-99.8), specificity of 62.5% (95% CI 47.3-75.7), NPV of 96.7% and failure rate of 3.3%).

Neutrophil count subanalyses according to the diagnosis of non-AD patients, type of dissection, and serial time interval change

Fig. 3 shows that the neutrophil counts in patients with AD were significantly higher than those in patients with acute coronary syndrome, atypical chest pain, or other diagnoses in the 2-24 h interval (neutrophil counts 11.7±5.4, 7.4±3.6, 6.3±2.9, 7.7±3.9, respectively). All P<0.001).

Neutrophil counts were also analyzed in patients with type A/B AD (Supplement Figure 1, Supplement Table 1). There was no significant difference in the neutrophil counts between patients with type A and B AD.

We further observed the trends in neutrophil counts among patients who had blood drawn multiple times to measure neutrophil counts. Twenty AD patients had neutrophil counts in both the 0-2 h and 2-24 h time intervals. The neutrophil counts increased from 6.4±3.4 (0-2 h) to 10.3±4.3 (2-24 h), with P<0.001 (Fig. 4).

Another 25 patients with AD had neutrophil counts at both the 2-24 h and >24 h time intervals. These neutrophil counts were similar (9.9±4.1 vs. 9.7±3.5, P=0.79, Suppl. Fig. 2).

Discussion

The results of this study suggested that neutrophil counts were higher in patients with AD during the time interval of 2–24 hours after symptom onset and may be used as an easily available biomarker to differentiate AD from other diseases. Within this time window, neutrophil counts ruled out aortic dissection with an NPV of 95.6% and a failure rate of 4.4%. This efficiency in ruling out aortic dissection remained static across groups with different ADD risk scores.

Several studies have indicated that the inflammatory response may play a critical role in AD initiation and progression[8, 11–14]. However, previous research mainly focused on the role of neutrophil counts in AD prognosis [8, 15–17] but not in AD diagnosis. In addition, the neutrophil/lymphocyte ratio (NLR) was commonly found to be increased in AD patients [15, 16, 18], but these studies used unsuitable control groups (healthy individuals), thus minimizing the efficiency. Zhang et al. used the neutrophil/lymphocyte ratio (NLR) as a tool for diagnosing AD-suspicious patients[9] but still faced some difficulty in calculating the ratio.

In a recent multicenter retrospective study, we measured the neutrophil counts of over 500 patients with suspected AD who underwent CT aortogram and used non-AD patients as the control group. The relatively large number of patients allowed us to perform subgroup analysis. One of the most important discoveries was that the neutrophil counts increased significantly 2 h after symptom onset and then decreased after 24 hours. Thus, we mainly focused on neutrophil counts in the 2–24 h time window. This may be the main reason why previous studies overlooked the diagnostic value of neutrophil counts.

According to our results, neutrophil counts peaked 2–24 hours after symptom onset. As expected, the neutrophil counts showed good ability to discriminate AD, with an AUC above 0.8, sensitivity of 95.6%

and specificity of 56.1%. The neutrophil counts were similar in patients with different types of AD and different ADD scores. Compared with previous studies [10, 19, 20], neutrophil counts were associated with mildly lower sensitivity and better specificity. Therefore, neutrophil counts may replace D-dimer levels in AD diagnosis within the 2–24 h time window.

There were major limitations in our research regarding this time window. The 2–24 h time window covered only approximately 45% of patients with suspected AD. Moreover, patients may not clearly remember the exact time of onset, and thus, it may not be possible to clearly elucidate the time interval.

Neutrophils were found in the aorta adventitial, and they were present there before 12 hours, peaked between 12 and 24 hours and were rarely found after 2 days [12]. These findings were partially supported by our results. In animal models, acute AD triggers CXCL1 and G-CSF expression in the adventitia of the aorta, leading to increased circulating CXCL1/G-CSF levels. These chemokines promote the mobilization of neutrophils from the bone marrow to the peripheral blood [21, 22]. Some time may be required for these chemical signals to recruit neutrophils to the blood. As a result, neutrophil counts remain static in the first 2 hours after symptom onset. The inflammatory response gradually decreases after the peak, and neutrophil counts return to normal.

In addition, the sensitivity of neutrophil counts is relatively lower than that of D-dimer levels [10, 19, 20]. D-dimer is derived from the degradation of fibrin in the false lumen of the aorta [23], which occurs immediately and directly after dissection and persists for days [24]. Compared with D-dimer levels, neutrophil counts are indirect indicators of AD and have less sensitivity.

Conclusion

A new approach that uses neutrophil counts within 2–24 h after symptom onset is of great value for ruling out aortic dissection during diagnostic work-up.

Abbreviations

aortic dissection (AD), aortic dissection detection (ADD)

Declarations

Ethics approval

The study was approved by the District (Kowloon Central/ Kowloon East Cluster) Ethics Boards (KC/KE-21-0222/ER-1). The requirements for informed consent were waved by District (Kowloon Central/ Kowloon East Cluster) Ethics Boards because this was a retrospective study; this study did not contain any personal identity data; this study did not influence the management and outcome of patients.

All methods were carried out in accordance with relevant guidelines and regulations or Declaration of Helsinki 1975 [25].

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Author's contributions

Dr. Chun and Dr. Siu made substantial contributions to the conception.

Acknowledgments

The authors would like to thank Dr. Kung, Shu Wing and Dr. Chan, Yiu Cheung for their generous help with this research.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

1. Tsai TT, Nienaber CA, Eagle KA. Acute aortic syndromes. Circulation. 2005;112(24):3802-13.
2. Meszaros I, Morocz J, Szlavi J, Schmidt J, Tornoci L, Nagy L, et al. Epidemiology and clinicopathology of aortic dissection. Chest. 2000;117(5):1271-8.
3. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE, Jr., et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation. 2010;121(13):e266-369.
4. Nazerian P, Morello F, Vanni S, Bono A, Castelli M, Forno D, et al. Combined use of aortic dissection detection risk score and D-dimer in the diagnostic workup of suspected acute aortic dissection. Int J Cardiol. 2014;175(1):78-82.

5. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(41):2873-926.
6. Li S, Yang J, Dong J, Guo R, Chang S, Zhu H, et al. Neutrophil to lymphocyte ratio and fibrinogen values in predicting patients with type B aortic dissection. Sci Rep. 2021;11(1):11366.
7. Yang Y, Sun G, Diao S, Yang L, Dong W. Diagnostic performances of neutrophil to lymphocyte ratio and lymphocyte to monocyte ratio in acute ischemic stroke caused by cervicocranial arterial dissection. J Clin Lab Anal. 2020;34(12):e23515.
8. Sbarouni E, Georgiadou P, Analitis A, Voudris V. High neutrophil to lymphocyte ratio in type A acute aortic dissection facilitates diagnosis and predicts worse outcome. Expert Rev Mol Diagn. 2015;15(7):965-70.
9. Zhang H, Guo J, Zhang Q, Yuan N, Chen Q, Guo Z, et al. The potential value of the neutrophil to lymphocyte ratio for early differential diagnosis and prognosis assessment in patients with aortic dissection. Clin Biochem. 2021;97:41-7.
10. Suzuki T, Distante A, Zizza A, Trimarchi S, Villani M, Salerno Uriarte JA, et al. Diagnosis of acute aortic dissection by D-dimer: the International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-Bio) experience. Circulation. 2009;119(20):2702-7.
11. Yoshida S, Yamamoto M, Aoki H, Fukuda H, Akasu K, Takagi K, et al. STAT3 Activation Correlates with Adventitial Neutrophil Infiltration in Human Aortic Dissection. Ann Vasc Dis. 2019;12(2):187-93.
12. Xu L, Burke A. Acute medial dissection of the ascending aorta: evolution of reactive histologic changes. Am J Surg Pathol. 2013;37(8):1275-82.
13. Suzuki K, Kimura N, Mieno M, Hori D, Sezai A, Yamaguchi A, et al. Factors related to white blood cell elevation in acute type A aortic dissection. PLoS One. 2020;15(2):e0228954.
14. Liu X, Wang G, Zhang T. The analysis of the levels of plasma inflammation-related cytokines and endotoxins in patients with acute aortic dissection. Clin Hemorheol Microcirc. 2020;76(1):1-7.
15. Kalkan ME, Kalkan AK, Gundes A, Yanartas M, Ozturk S, Gurbuz AS, et al. Neutrophil to lymphocyte ratio: a novel marker for predicting hospital mortality of patients with acute type A aortic dissection. Perfusion. 2017;32(4):321-7.
16. Xu Y, Fang H, Qiu Z, Cheng X. Prognostic role of neutrophil-to-lymphocyte ratio in aortic disease: a meta-analysis of observational studies. J Cardiothorac Surg. 2020;15(1):215.
17. Onuk T, Gungor B, Karatas B, Ipek G, Akyuz S, Ozcan KS, et al. Increased Neutrophil to Lymphocyte Ratio is Associated with In-Hospital Mortality in Patients with Aortic Dissection. Clin Lab. 2015;61(9):1275-82.
18. Erdolu B, As AK. C-Reactive Protein and Neutrophil to Lymphocyte Ratio Values in Predicting Inhospital Death in Patients with Stanford Type A Acute Aortic Dissection. Heart Surg Forum. 2020;23(4):E488-E92.

19. Nazerian P, Mueller C, Soeiro AM, Leidel BA, Salvadeo SAT, Giachino F, et al. Diagnostic Accuracy of the Aortic Dissection Detection Risk Score Plus D-Dimer for Acute Aortic Syndromes: The ADvISED Prospective Multicenter Study. Circulation. 2018;137(3):250-8.
20. Koch V, Biener M, Muller-Hennessen M, Vafaie M, Staudacher I, Katus HA, et al. Diagnostic performance of D-dimer in predicting venous thromboembolism and acute aortic dissection. Eur Heart J Acute Cardiovasc Care. 2020
21. Anzai A, Shimoda M, Endo J, Kohno T, Katsumata Y, Matsuhashi T, et al. Adventitial CXCL1/G-CSF expression in response to acute aortic dissection triggers local neutrophil recruitment and activation leading to aortic rupture. Circ Res. 2015;116(4):612-23.
22. Kurihara T, Shimizu-Hirota R, Shimoda M, Adachi T, Shimizu H, Weiss SJ, et al. Neutrophil-derived matrix metalloproteinase 9 triggers acute aortic dissection. Circulation. 2012;126(25):3070-80.
23. Eggebrecht H, Naber CK, Bruch C, Kroger K, von Birgelen C, Schmermund A, et al. Value of plasma fibrin D-dimers for detection of acute aortic dissection. J Am Coll Cardiol. 2004;44(4):804-9.
24. Albini P, Barshes NR, Russell L, Wu D, Coselli JS, Shen YH, et al. D-dimer levels remain elevated in acute aortic dissection after 24 h. J Surg Res. 2014;191(1):58-63.
25. Shephard DA. The 1975 Declaration of Helsinki and consent. *Can Med Assoc J*. 1976;115(12):1191-1192.

Tables

Table 1

Patients demographics and prevalence of the ADD risk markers

	Overall (n=534, 100%)	AD (n=198, 37.1%)	Non AD (n=336, 62.9%)	P
Demographic				
Age (years)	65.2±14.6	66.0±15.1	63.7±13.8	0.07
male	326 (61.0%)	136 (69.2%)	190 (56.5%)	0.005
Systolic blood pressure (mmHg)	146.7±40.8	143.5±42.6	148.7±39.5	0.10
Heart rate (bpm)	79.6±19.4	75.8±18.9	81.9±19.4	<0.001
Past medical histories				
Arterial hypertension	253 (47.4%)	88 (44.4%)	165 (49.1%)	0.25
Diabetes	76 (14.2%)	17 (8.6%)	59 (17.6%)	0.004
Hyperlipidemia	60 (11.2%)	18 (9.1%)	42 (12.5%)	0.22
Ischemic heart disease	56 (10.5%)	6 (3.0%)	50 (13.9%)	<0.001
stroke	29 (5.4%)	5 (2.5%)	24 (7.1%)	0.023
ADD risk marker				
Predisposing condition	49 (5.2%)	27 (13.6%)	22 (6.5%)	0.007
Marfan	7 (1.3%)	5 (2.5%)	3 (0.9%)	0.15
Family history of aortic disease	2 (0.4%)	2 (0.1%)	0 (0%)	0.14
Known aortic valve disease	3 (0.6%)	1 (0.1%)	2 (0.1%)	0.69
Recent aortic manipulation	24 (4.5%)	12 (6.1%)	12 (3.6%)	0.20
Known thoracic aortic aneurysm	17 (3.2%)	10 (5.1%)	7 (2.1%)	0.06
Pain features	395 (74.0%)	156 (78.8%)	239 (71.1%)	0.051
Abrupt onset of pain	345 (64.6%)	137 (69.2%)	208 (61.9)	0.09
Severe pain intensity	257 (48.1%)	100 (50.5%)	157 (46.7%)	0.40
Ripping or tearing pain	25 (4.7%)	12 (6.1%)	13 (3.9%)	0.25
Physical findings	158 (29.6%)	60 (30.3%)	98 (29.2%)	0.78
Pulse deficit or SBP differential	83 (15.5%)	22 (11.1%)	61 (18.1%)	0.03
Focal neurological deficit	39 (7.3%)	17 (8.6%)	21 (6.3%)	0.32
Murmur of aortic insufficiency	2 (0.3%)	2 (1.0%)	0 (0%)	0.14

Hypotension or shock state	47 (8.8%)	24 (12.1%)	23 (6.8%)	0.04

Table 2

Patients distribution of time intervals between symptoms onset and bloods taken

Time	Overall (n=534, 100%)	AD (n=198, 37.1%)	Non AD (n=336, 62.9%)
0-2h	149 (27.9%)	64 (32.3%)	85 (25.3%)
2-8h	174 (32.6%)	58 (29.3%)	116 (34.5%)
8-24h	72 (13.5%)	32 (16.2%)	40 (11.9%)
24h-7 days	94 (17.6%)	27 (13.6%)	67 (19.9%)
> one week	45 (8.4%)	17 (8.6%)	28 (8.3%)
Merge group			
2-24h	246 (46.1%)	90 (45.4%)	156 (46.4%)
>1d	139 (26.0%)	44 (22.2%)	95 (28.3%)

Table 3

ADD risk score in the study population

ADD risk score	Overall (n=534, 100%)	AD (n=198, 37.1%)	Non AD (n=336, 62.9%)
0	48 (9.0%)	14 (7.1%)	34 (10.1%)
1	334 (62.5%)	116 (58.6%)	218 (64.9%)
2	148 (27.7%)	65 (32.8%)	83 (27.4%)
3	4 (0.7%)	3 (1.5%)	1 (0.3%)
Low probability (score≤1)	382 (71.5%)	130 (65.6%)	252 (75.0%)
High probility (score>1)	152 (28.5%)	68 (34.3%)	84 (25.0%)

Table 4

Diagnostic accuracy of neutrophil count (cutoff $6.2*10^9$/L) in patient groups

	Sensitivity % CI	Specificity % CI	PLR	NLR	PPV	NPV
overall	69.2 (62.2-75.4)	56.0 (50.5-61.3)	1.57	0.55	48.1	75.5
0-2h	45.3 (33.0-58.2)	63.5 (52.3-73.5)	1.24	0.86	48.3	60.7
2-8h	94.8 (84.7-98.6)	59.4 (50.0-68.4)	2.34	0.09	53.9	95.8
8-24h	96.9 (82.0-99.8)	45.0 (29.6-61.3)	1.76	0.07	58.5	94.7
1-7d	59.3 (39.0-77.0)	51.5 (39.1-63.6)	1.22	0.79	32.7	76.1
>1w	35.3 (15.3-61.4)	50.0 (31.1-68.9)	0.71	1.29	30.0	56.0

Table 5

Diagnostic performance of Neutrophil at a cutoff value of 6.2 according to ADD risk score in patients with 2-24h after symptoms onset

Patients	Sensitivity % CI	Specificity % CI	PLR	NLR	PPV	NPV
All with high neutrophil	95.6 (88.4-98.6)	56.1 (47.9-63.9)	2.71	0.08	55.5	95.6
ADD>1	34.3 (27.8-41.5)	75.0 (69.9-79.5)	1.37	0.87	44.7	66.0
ADD≦1with high neutrophil	94.6 (84.2-98.6)	52.3 (42.1-61.9)	1.98	0.10	50.4	95.0
ADD>1 with high neutrophil	97.1 (82.9-99.8)	62.5 (47.3-75.7)	2.58	0.05	64.7	96.7

Figures

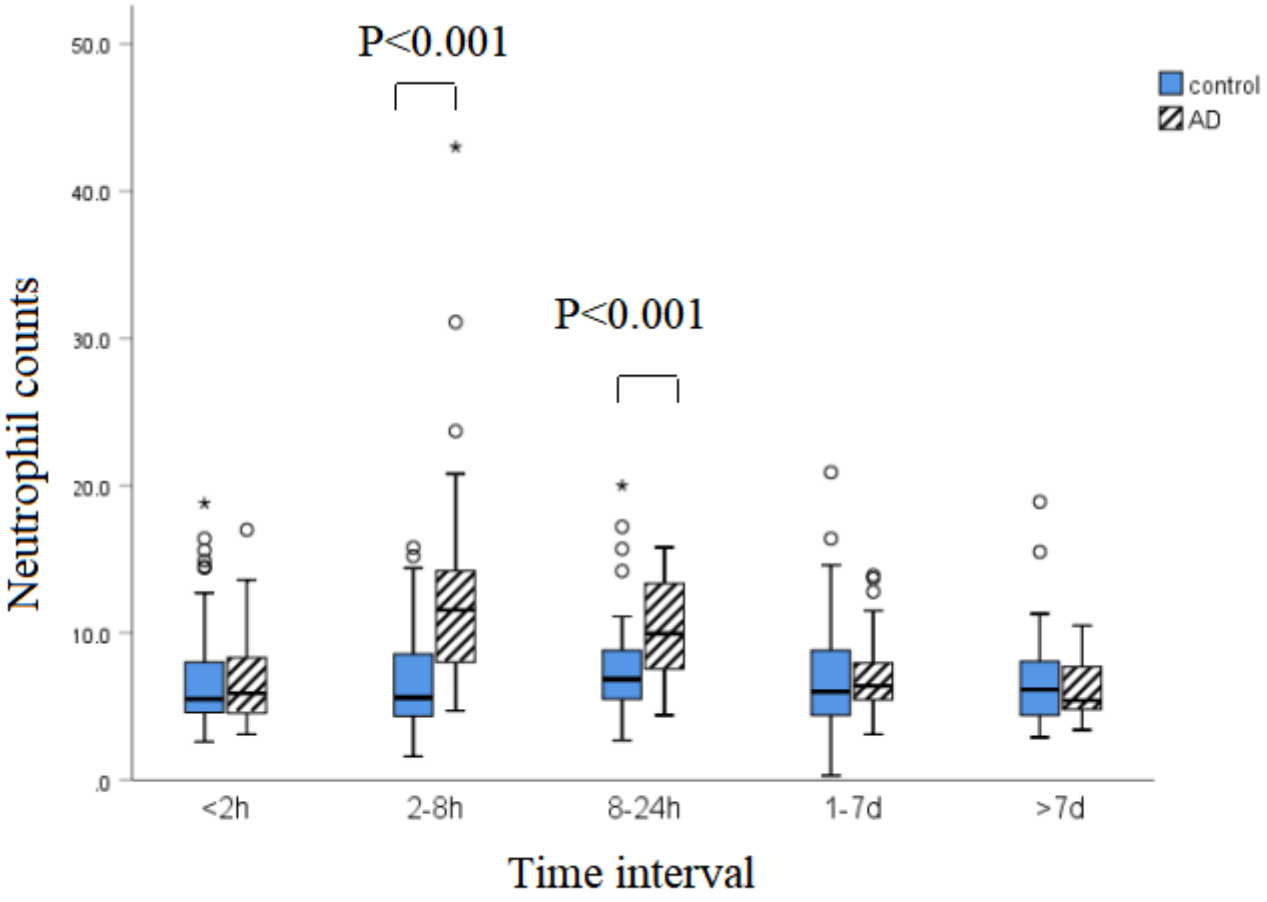

Figure 1

Time course box plots of neutrophil levels in patients according to time from symptom onset

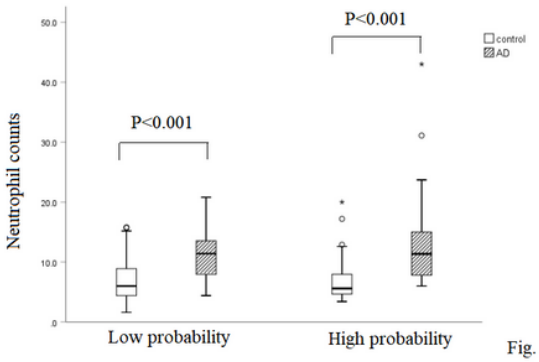

Fig. 2a

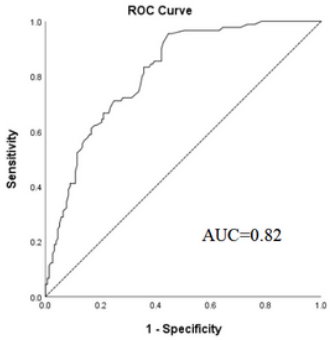

Fig. 2b

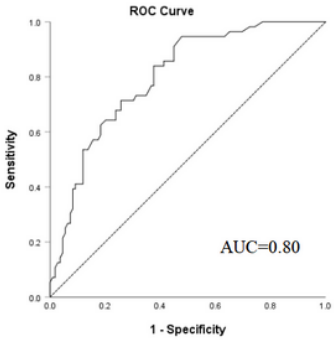

Fig. 2c

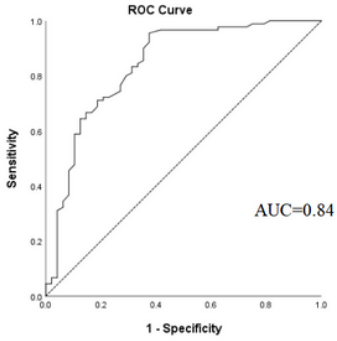

Fig. 2d

Figure 2

Neutrophil counts according to the AAD risk score in the 2-24 hr time interval group (a), curve analysis showing the diagnostic value of neutrophil counts for identifying patients with AD among the total patient population (2-24 h interval) (b) and in those with low probability scores (c) and high probability scores (d).

AUC: area under the curve; CI confidence interval

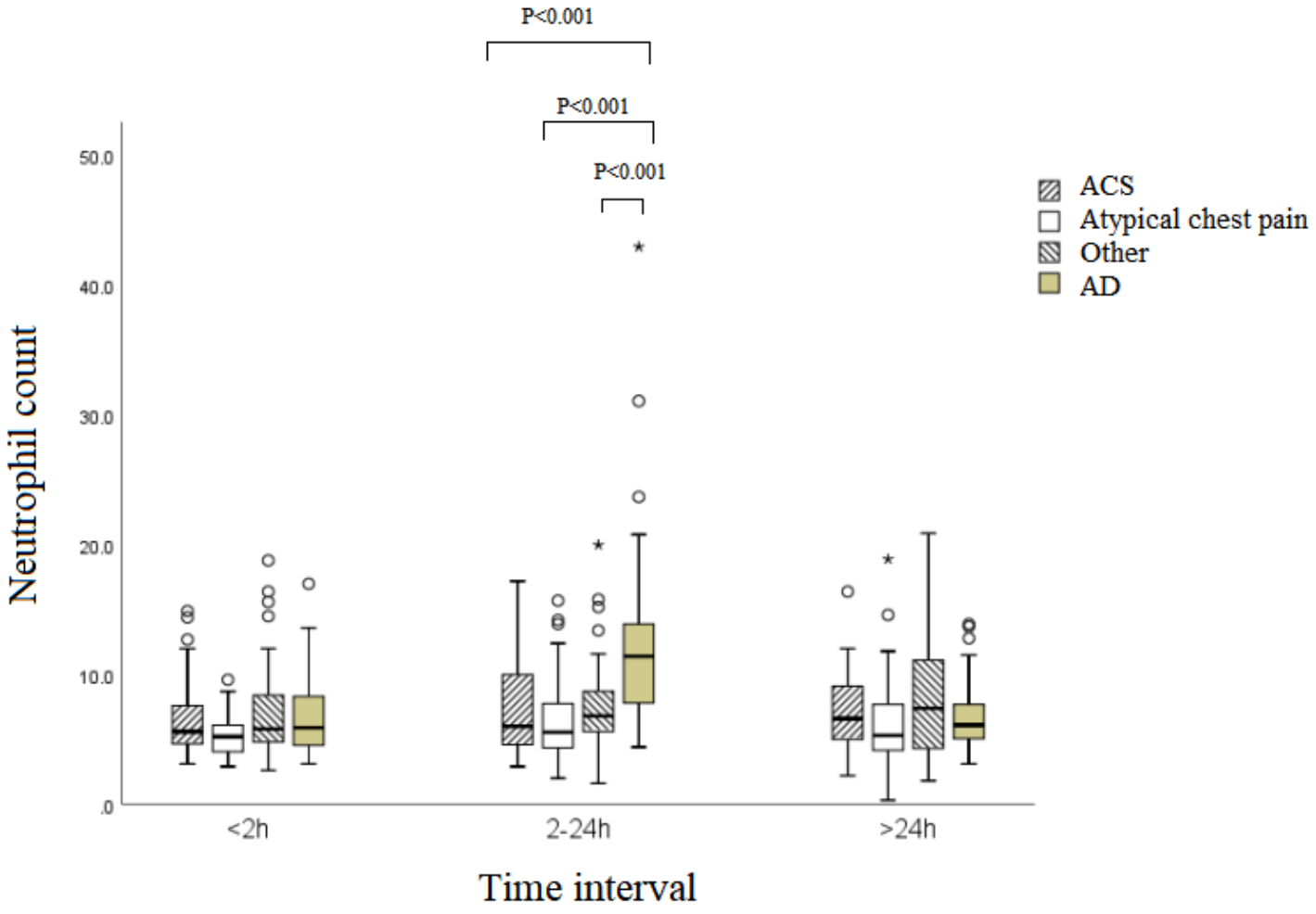

Figure 3

Box plots of neutrophil counts in patients with different diagnoses according to time interval

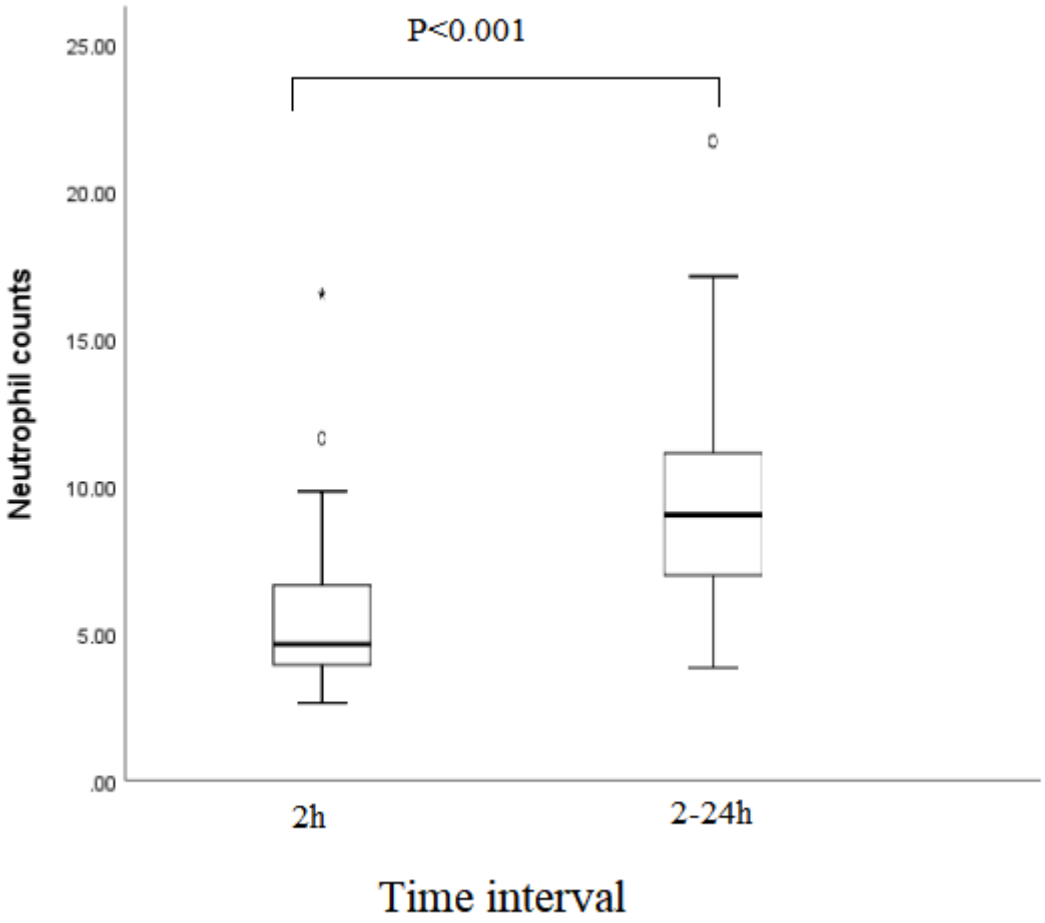

Figure 4

Neutrophil counts in 25 patients with serial neutrophil results (<2 h and 2-24 h)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supp.Fig1.bmp
- supp.Fig2.bmp
- Supp.Table1.docx