Post hoc labeling an acute ECG as ischemic or non-ischemic based on clinical data: a necessary challenge

Haar, C.C. ter; Swenne, C.A.

Journal of Electrocardiology 81 (2023) 75–79

Contents lists available at ScienceDirect

Journal of Electrocardiology

journal homepage: www.jecgonline.com

Post hoc labeling an acute ECG as ischemic or non-ischemic based on clinical data: A necessary challenge

C. Cato ter Haar [a,b,*], Cees A. Swenne [b]

[a] Cardiology Department, Amsterdam University Medical Center, Amsterdam, The Netherlands
[b] Cardiology Department, Leiden University Medical Center, Leiden, The Netherlands

ARTICLE INFO

Keywords:
Myocardial ischemia
Acute coronary syndrome
Acute ECG
Prehospital ECG

ABSTRACT

The ECG is crucial in the prehospital (and early inhospital) phase of patients with symptoms suggestive of myocardial ischemia. Therefore, new algorithms for ECG-based myocardial ischemia detection are continuously being researched. Development and validation of these algorithms require a database of acute ECGs (from the prehospital or emergency department setting) including a representative mix of cases (ischemia present) and controls (no ischemia present). Therefore, for every patient in this mix, the "truth" regarding the actual presence or absence of myocardial ischemia during the recording of the acute ECG has to be determined to compare the newly developed algorithm against. This post hoc adjudication process of determining whether an acute (either prehospitally acquired or acquired in the emergency department) ECG was made under ischemic conditions should use all available clinical data (the clinical diagnosis, cardiac imaging data, and laboratory values) of the subsequent patient's admission.

Even with all data at hand, post hoc labeling a patient and their acute ECG as a myocardial ischemia case or control cannot be forced into a binary division between definite cases and definite controls. More specifically, to be used for the development of a new algorithm, the patients' ECG has to be scored for the presence or absence of myocardial ischemia at the exact moment of its recording, which renders the classification even more difficult. For instance, even though it may be plausible that myocardial ischemia was present at a given moment during the patient's admission, this is not necessarily proof that the prehospital (or early inhospital) ECG was also made in ischemic conditions: ischemia can be a fluctuating process (as is, e.g., the case in unstable angina pectoris). Therefore, post hoc classification of an acute ECG in terms of the absence or presence of ischemia requires a multipoint scale ranging between definite ischemic to definite non-ischemic, for instance using a 5-point scale (presumed non-ischemic, probably non-ischemic, uncertain, probably ischemic, presumed ischemic).

To summarize, the post hoc adjudication process of ECGs of ambulance (and emergency department) patients cannot result in a binary division into definite cases and controls (i.e., patients with or without myocardial ischemia during the recording of the acute ECG), as myocardial ischemia is often dynamic rather than constant. ECGs could be labeled on a multi-point scale, in which the label represents the probability of the actual presence (or absence) of myocardial ischemia at the exact moment of the recording of that ECG. Further development of algorithms for myocardial ischemia detection should consider this concept.

Introduction

When patients present to the emergency medical services (EMS)/ambulance (prehospital) or at the emergency department (ED, early inhospital) with symptoms suggestive of myocardial ischemia, e.g., chest pain, myocardial ischemia needs to be ruled in or out for accurate triage and treatment. At one end of the spectrum, occlusion of a large coronary artery obviously necessitates swift presentation to (a hospital with) cardiac catheterization facilities. However, at the other end of the spectrum, the vast majority of patients does not have myocardial ischemia [1] and can be transported to another (non-cardiac) department, go/stay home, or go to the general practitioner.

In the case of suspected myocardial ischemia, the ECG, being an objective tool, is routinely used in accordance with guideline recommendations [2–4]. Therefore, new algorithms for ECG-based myocardial ischemia detection are continuously being explored.

* Corresponding author at: Revaleiland 93, 1014ZG Amsterdam, The Netherlands.
E-mail address: c.c.terhaar@amsterdamumc.nl (C.C. ter Haar).

https://doi.org/10.1016/j.jelectrocard.2023.08.007

Available online 19 August 2023

Developing and validating such a myocardial ischemia detection algorithm requires a database that contains a representative mix of cases (ischemia present in the ECG) and controls (no ischemia present). Such a database consists of acute ECGs made in ambulance (prehospital phase) or ED (early inhospital phase) patients. To discover myocardial ischemia-induced ECG changes, these ECG changes have to be compared to whether or not the patient was actually ischemic during the recording of that ECG. Therefore, for each patient, and more specifically for each ECG, the "ground truth" regarding the presence or absence of myocardial ischemia has to be determined (i.e., during that specific time point of the recording of that ECG). This truth regarding the actual presence of myocardial ischemia during the recording of the acute ECG can only be found by retrospectively reviewing each patient with all clinical data of the subsequent admission of the patient (e.g., if a patient was admitted and was appointed a myocardial infarction diagnosis, it is presumable that the earlier acquired acute ECG was made under ischemic conditions).

However, this post hoc adjudication process can be challenging, especially if a database representative of the real-life situation is used, i.e., including more than only the clear-cut cases on the outer edges of the myocardial ischemia spectrum (e.g., STEMI vs hyperventilation syndrome). In this article, we discuss the possibilities and impossibilities of post hoc adjudication of the acute (either ambulance/prehospital or ED) ECG in a database that has to facilitate development and testing of new computer algorithms for myocardial ischemia detection. Additionally, we provide recommendations and an example on how such a post hoc myocardial ischemia classification algorithm can be put together, as we did in earlier research [1].

Approach for a post hoc myocardial ischemia classification algorithm

Post hoc classification of an patient presenting either at the EMS or at the ED and their ECG at that moment of first medical contact (the acute ECG) as ischemic or non-ischemic should use all clinical data that are collected during the subsequent admission of that patient. We herewith outline and discuss the usefulness of the most relevant clinical data. Subsequently, we recommend how these data can be incorporated into the post hoc adjudication process and how the myocardial ischemia classification algorithm can be designed. Off note, labeling a patient as ischemic or non-ischemic is easier than labeling their acute ECG. However, for the development of a new ECG algorithm, one needs to know whether that specific ECG was made under ischemic circumstances, not only whether the patient was ischemic at one point during their admission. We, therefore, focus on and emphasize labeling the acute ECGs rather than the patients themselves.

Contribution of clinical data to the post hoc ischemia labeling of acute ECGs

Clinical diagnosis

In post-hoc labeling of the acute ECG for the presence of myocardial ischemia, the clinical diagnosis should be the leading factor. The clinical diagnosis is established by the treating physician during or at the end of the patient's admission, after initial medical history taking, physical examination, and reviewing of the subsequently made in-hospital ECG(s), laboratory results, (cardiac) imaging data, and the clinical course during admission. Despite inter-physician variability, the clinical diagnosis contains the most reliable information for post hoc ischemia labeling of the acute ECG. Because it is an expert opinion, the interpretation by the treating doctor has added value to the other data that can be retrieved from the medical records. However, since errors cannot completely be avoided in clinical practice, the plausibility of the clinical diagnosis should always be checked by an expert panel using all available clinical data, briefly discussed below.

ECGs

All ECGs acquired from a patient presenting to the EMS or ED include valuable information. Especially, serial ECG changes (prehospital-prehospital, prehospital-inhospital and inhospital-inhospital) could retrospectively add evidence for the presence of myocardial ischemia [5,6].

Of note, strictly methodologically seen, an independent post hoc assessment of the presence or absence of myocardial ischemia in the acute ECG would require that the ECG itself be left out of consideration and that, ideally, only subsequently recorded inhospital ECGs should be taken into account. In clinical reality, however, the physician's overall (ECG) interpretation will inevitably also be based on all available ECGs, including the acute ECG.

Additionally, whether or not symptoms were present during the instant of the recording of the acute ECG could prove helpful in myocardial ischemia classification by providing additional information in situations with fluctuating degrees of ischemia (i.e., the patient has episodes of myocardial ischemia, but it is unknown whether it was present during the recording of that ECG). Ideally, the patient's pain score should be digitally entered as a comment and saved together with the ECG to be incorporated into the myocardial ischemia classification.

Laboratory values

Recent myocardial necrosis can be assessed in blood by measuring cardiac troponin levels with high sensitivity [2–4]. Moreover, cardiac troponin levels are objective, often available, and allow for different cut-off values to be used depending on the clinical diagnosis (e.g., troponin levels can discriminate between cardiac decompensation with or without myocardial ischemia). However, myocardial ischemia does not always induce necrosis, and if it does, it takes time [7,8]; it takes even more time for troponin proteins to be released in the bloodstream. Hence, the usefulness of this laboratory value is limited for the purpose of (acute) myocardial ischemia detection.

Obviously, since the adjudication process is done retrospectively, all troponin values measured during the patients' admission can be used; hence it is less important that it takes time for troponins to become positive. However, cardiac troponin merely tells you that necrosis (and hence myocardial ischemia) has occurred at some time before, but not at which point in time exactly (thus, it is unknown whether it was already/still present during the recording of the acute ECG). Moreover, in the case of unstable angina pectoris (UAP) there is a by definition a discrepancy between the presence of myocardial ischemia and the elevation of troponins [9]. Additionally, troponin levels are often elevated due to non-coronary or even non-cardiac diseases, e.g., perimyocarditis and rhabdomyolysis [10], resulting in possible false positives.

Renal function affects troponin levels due to impaired excretion, therefore before troponin levels can be interpreted, they must be corrected for renal function [11,12]. Since different troponin types and different assays are used in various hospitals [9], we recommend to adhere to the hospital's protocol for determining the cutoff values for the presence of cardiac ischemia.

Cardiac imaging

In the myocardial ischemic cascade, wall motion abnormalities precede ECG changes and even symptoms [7,8] and are therefore a useful tool for myocardial ischemia detection. However, evaluating a cardiac ultrasound regarding (new) wall motion abnormalities is difficult and time consuming and is therefore reserved to be performed and interpreted by a specialist. The results of a cardiac ultrasound measurement can however aid in checking the diagnosis by discriminating regional wall abnormalities (myocardial ischemia) from generalized wall abnormalities (heart failure).

Secondly, as the gold standard for epicardial coronary obstruction, cardiac catheterization results (in case available) can be used to check the clinical diagnosis. Unfortunately (in terms of information), but logically (in terms of medical decision-making), only a small percentage

of patients presenting with chest pain undergo cardiac catheterization during the subsequent hospital admission. Moreover, the time delay between the recording of the prehospital or early inhospital ECG and the cardiac catheterization could cloud their association. Hence, catheterization data are only playing a role in a minority of the patients in whom a post hoc assessment of the absence or presence of ischemia in an acute ECG is to be made.

Incorporation of clinical data obtained during admission into the myocardial ischemia classification algorithm

As stated above, the myocardial ischemia classification algorithm for post hoc adjudication of an ambulance or ED patient and their acute ECG should, in the first place, rest on the clinical diagnosis as assessed by the responsible physician. The clinical data obtained during the admission of the patient are particularly useful for checking the plausibility of the clinical diagnosis.

Importantly, if the treating physician's clinical diagnosis does not necessarily involve myocardial ischemia, as is, e.g., the case in pulmonary embolism, an expert panel should use the clinical data for the myocardial ischemia classification of the acute ECG. For instance, troponin values measured during the initial hours, by reflecting cardiac necrosis, can aid in retrospectively evaluating whether there would have been (persistent) myocardial ischemia present during the recording of the acute ECG in other than primarily coronary-related diagnoses, e.g., cardiac decompensation with elevated troponin levels. This adjudication process of difficult cases should be done by an expert panel.

Multi-point scale myocardial ischemia classification algorithm

Since in medical practice, even with all data at hand, not all diagnoses can be made with complete certainty, the post hoc adjudication process also cannot result in a binary division into definite cases and controls (i.e., patients with or without myocardial ischemia during the recording of the acute ECG). Obviously, the two extremes of the myocardial ischemia spectrum are easy to defend (STEMI vs hyperventilation syndrome). However, what about the cases in-between [13], in which the balance of coronary supply and demand is disrupted, e.g., severe sepsis with mildly elevated troponin levels. Moreover, even though it may be plausible that myocardial ischemia was present at a given moment during the patient's admission, and hence the patient itself is a myocardial ischemia case, this is not necessarily proof that the acute ECG was made in ischemic conditions, as myocardial ischemia is often dynamic rather than constant.

Hence, adequate post hoc labeling of an acute ECG in terms of the absence or presence of ischemia requires a multipoint scale, to be able to label, in addition to the clear-cut cases (most likely ischemic) and controls (most likely non-ischemic), the less certain cases (probably ischemic) and controls (probably non ischemic), and the unknown ECGs (for instance, with the clinical diagnosis unstable angina, the acute ECG may have been made during an ischemic episode or not). In summary: a 5-point scale: presumed non-ischemic (most likely non-ischemic), probably non-ischemic, uncertain, probably ischemic, and presumed ischemic (most likely ischemic) [1]. Fig. 1 provides an example of different diagnoses could fit into the myocardial ischemia spectrum.

An example of a post hoc ischemia classification algorithm for acute ECGs

Until here, we described the guiding principles for an algorithm to classify acute ECGs as ischemic or not on a 5-point scale. The actual realization of such an algorithm requires ample discussions of a large spectrum of clinical cases involved in the evaluation of chest pain with an eye on ischemia as one possible cause of chest pain or discomfort. To demonstrate what the probable result of such a discussion could practically imply, we summarize in the following example how we have realized and used such a post hoc ischemia classification algorithm in our own research [1].

Classification "Presumed ischemic": Clinical diagnoses where either necrosis is inherent to the diagnosis, e.g., ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI), i.e., any type of myocardial infarction, or if the diagnosis could involve myocardial ischemia, e.g., pulmonary embolism, in combination with supporting evidence for myocardial necrosis (elevated troponin levels and/or positive cardiac imaging) [14].

Classification "Probably ischemic": Clinical diagnoses that could involve myocardial ischemia, in combination with troponin levels or imaging results that are slightly, but not clearly, pointing in the direction of myocardial necrosis, e.g., cardiac decompensation with moderately elevated troponin levels [15].

Classification "Uncertain": Assigned in case of insufficient diagnostics or if the actual occurrence of ischemia during the recording of the acute ECG remains unknown due to presumed fluctuations in myocardial perfusion, e.g., with the diagnosis of unstable angina pectoris [16].

Classification "Probably nonischemic": Clinical diagnoses that could be associated with myocardial ischemia, but neither troponin levels nor cardiac imaging results were available to definitely exclude myocardial

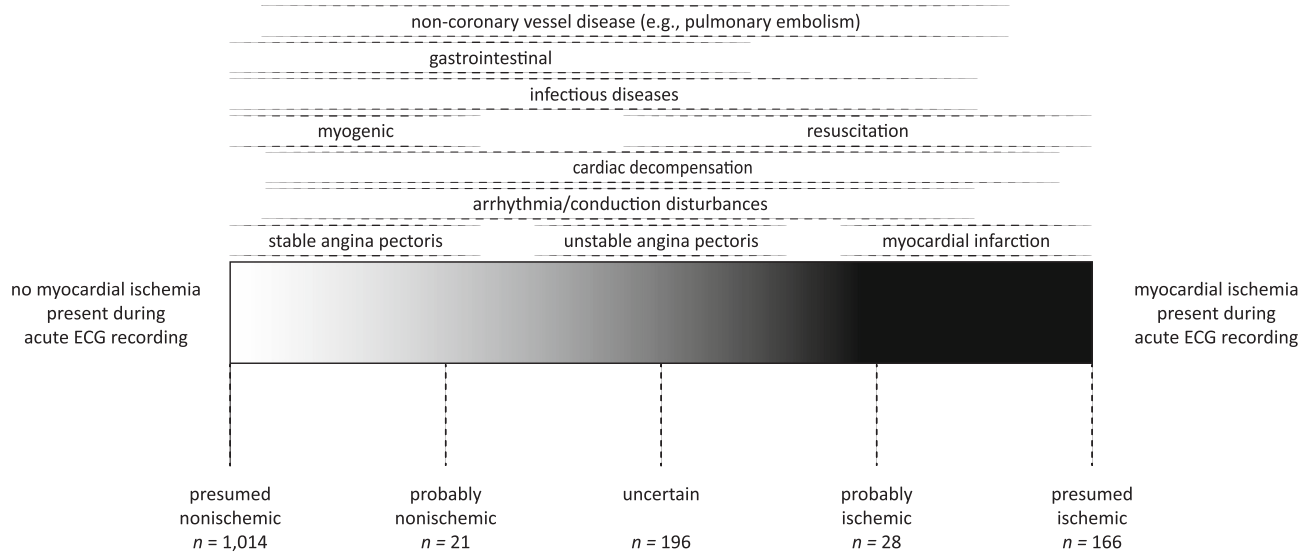

Fig. 1. Certainty of the presence of myocardial ischemia during recording of the acute ECG: a spectrum.

ischemia, e.g., severe pneumothorax [17], with a single nonrepresentative low troponin level; in this case, myocardial ischemia cannot be excluded, and hence the resulting classification is "probably nonischemic."

Classification "Presumed nonischemic": Clinical diagnoses that are not associated with myocardial ischemia, e.g., hyperventilation syndrome, or possibly associated with myocardial ischemia but for which there is no support by the troponin levels and/or imaging, e.g., cardiac decompensation with negative representative troponin levels.

Again, as an example, we achieved the following diagnostic spectrum in our recent study [1]. In this study, we post hoc labeled the prehospital/ambulance ECGs of patients who were urgently attended by the EMS because of chest pain for the purpose of ruling-in or ruling-out myocardial ischemia. A total of 1425 patients were included, of these 166 had presumed ischemia, 28 had probably ischemia, 196 patients were classified as uncertain (no convincing evidence for either presence or absence of ischemia), 21 were probably nonischemic, and 1014 were presumed nonischemic (see also Fig. 1).

Discussion

Uncertainty

No matter how much effort one puts into adjudicating acute ECGs on the basis of post hoc clinical data, it is unlikely that ECGs can be labeled as ischemic or non-ischemic with absolute certainty. This is especially the case when the database includes (albeit necessary for the representativity for clinical practice) the complete spectrum of myocardial ischemia, which is broader than acute coronary syndrome only. No myocardial ischemia classification algorithm is perfect. However, by avoiding bias and endorsing the algorithm's reproducibility, even a slightly imperfect algorithm could be of great use.

In fact, the advantage of using "uncertain" and "probable" classes is that it allows for doubtful cases to be properly classified, in accordance with medical practice in which not every diagnosis is completely certain. Without uncertain and probable classes, such cases would have been wrongly forced into a binary classification. Off note, in case the development of a new ECG-based myocardial ischemia classification algorithm would require a binary input, the presumed and probable cases and the presumed and probable controls on the 5-point scale could be combined into two classes, cases and controls; the uncertain category would have to be excluded, however.

Troponin values and renal function

Renal excretion of cardiac troponin is impaired in patients with kidney failure. However, the guidelines state not to correct cardiac troponins for renal function because it is not proven that a better balance between safety and efficacy could be achieved [9]. Contrastingly, in clinical practice, correction is often actually still done by the treating physician, understandably, since troponin values are gravely affected by renal function [18]. Therefore, in our opinion, for scientific purposes, such a correction must be done somehow; for a myocardial ischemia classification algorithm this could, e.g., be done by linear correction [11], or with modified cut-off values [12].

Type 1 (supply) and type 2 (demand) myocardial ischemia

Myocardial ischemia type 1 (myocardial ischemia due to a deprivation of coronary blood supply) [19] and type 2 (myocardial ischemia due to an increased demand of coronary blood supply) [19] require different treatments. This poses a gigantic challenge however, because the myocardial ischemia could be due to multiple factors or a combination of factors (e.g., plaque rupture with coronary spasm, fulminant cardiac decompensation due to myocardial ischemia). Moreover, the gold standard for assessing myocardial infarction type 1 is cardiac catheterization in which often, especially in the less clear-cut cases, a large time gap exists between the recording of the prehospital or, to a lesser extent, the early inhospital ECG and the cardiac catheterization procedure. During this time, symptoms and ECGs can fluctuate, or there is no cardiac catheterization performed during that hospital admission at all. Additionally, patients with either type of myocardial ischemia should anyway be transferred to a hospital. Therefore, the first step in the development of myocardial ischemia detection algorithms in the acute ECG should be the recognition of myocardial ischemia of any cause. Next steps could include algorithmic refinements to discriminate between type 1 or type 2 ischemia [19].

Conclusions

In order to continue improving (pre)hospital health care, the development of algorithms for myocardial ischemia detection in the acute ECG requires representative databases consisting of ambulance or ED patients' ECGs, each with a post hoc adjudicated multipoint-scale ischemia label based on the clinical data obtained from the patient's subsequent admission.

Whether or not myocardial ischemia was presence during the recording of the acute ECG cannot be forced into a binary division, hence is not black and white, but can better be classified on a spectrum. Examples of various (groups of) diagnoses and how these diagnoses could be placed on the myocardial ischemia certainty spectrum are depicted in this figure. Off note, these diagnoses are meant as an example and do not include the complete differential diagnosis of patients with complaints suggestive of myocardial ischemia. Below the figure is the 5-point scale as an example as used in our earlier research with the corresponding number of patients in each class [1].

Author statement

C. Cato ter Haar wrote the manuscript with large help from Cees A. Swenne.

References

[1] Ter Haar CC, Peters RJG, Bosch J, et al. An initial exploration of subtraction electrocardiography to detect myocardial ischemia in the prehospital setting. Ann Noninvasive Electrocardiol 2020;25(3):e12722.
[2] Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. Circulation. 2021;144(22):e368–454.
[3] Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2017;39:119–77.
[4] O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. Circulation. 2013;127(4):e362–425.
[5] Bouzid Z, Faramand Z, Martin-Gill C, et al. Incorporation of serial 12-Lead electrocardiogram with machine learning to augment the out-of-hospital diagnosis of non-ST elevation acute coronary syndrome. Ann Emerg Med 2023;81(1):57–69.
[6] Silber SH, Leo PJ, Katapadi M. Serial electrocardiograms for chest pain patients with initial nondiagnostic electrocardiograms: implications for thrombolytic therapy. Acad Emerg Med 1996;3(2):147–52.
[7] Seitun S, Castiglione Morelli M, Budaj I, et al. Stress computed tomography myocardial perfusion imaging: a new topic in cardiology. Rev Esp Cardiol (Engl Ed) 2016;69(2):188–200.
[8] Beller GA. Myocardial perfusion imaging for detection of silent myocardial ischemia. Am J Cardiol 1988;61(12):22F–8F.
[9] Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2021;42(14):1289–367.
[10] Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the Management of Acute Coronary Syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37(3):267–315.
[11] Friden V, Starnberg K, Muslimovic A, et al. Clearance of cardiac troponin T with and without kidney function. Clin Biochem 2017;50(9):468–74.

[12] Kampmann J, Heaf J, Backer Mogensen C, et al. Troponin cut-offs for acute myocardial infarction in patients with impaired renal function-a systematic review and Meta-analysis. Diagnostics (Basel) 2022;12(2).
[13] Al-Zaiti S, Macleod R, Dam PV, Smith SW, Birnbaum Y. Emerging ECG methods for acute coronary syndrome detection: recommendations & future opportunities. J Electrocardiol 2022;74:65–72.
[14] Douketis JD, Crowther MA, Stanton EB, Ginsberg JS. Elevated cardiac troponin levels in patients with submassive pulmonary embolism. Arch Intern Med 2002; 162(1):79–81.
[15] Januzzi Jr JL, Filippatos G, Nieminen M, Gheorghiade M. Troponin elevation in patients with heart failure: on behalf of the third universal definition of myocardial infarction global task force: heart failure section. Eur Heart J 2012;33(18): 2265–71.
[16] Sheridan PJ, Crossman DC. Critical review of unstable angina and non-ST elevation myocardial infarction. Postgrad Med J 2002;78(926):717–26.
[17] Janssens U, Koch KC, Graf J, Hanrath P. Severe transmyocardial ischemia in a patient with tension pneumothorax. Crit Care Med 2000;28(5):1638–41.
[18] Gunsolus I, Sandoval Y, Smith SW, et al. Renal dysfunction influences the diagnostic and prognostic performance of high-sensitivity cardiac troponin I. J Am Soc Nephrol 2018;29(2):636–43.
[19] Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Circulation. 2018;138(20):e618–51.