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Impact of more conservative European Society of Cardiology guidelines on the management of patients with acute chest pain

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Abstract

Objective: Early diagnosis or rule-out of acute coronary syndrome (ACS) is a key competence of emergency medicine. Changes in the NSTE-ACS guidelines of the European Society of Cardiology (ESC) in 2015 and 2020 both warranted a henceforth more conservative approach regarding high-sensitivity troponin t (hsTnt) testing.

We aimed to assess the impact of more conservative guidelines on the frequency of early rule-out and prolonged observation with repeated hsTnt testing at a high-volume tertiary care emergency department.

Patients and Methods: We conducted a pre- and post-changeover analysis 3 months before and 3 months after transition from less (hsTnt cut-off 30 ng/L, 3-hour rule-out) to more conservative (hsTnt cut-off 14 ng/L, 1-hour rule-out) guidelines in 2015, comparing proportions of patients requiring repeated testing.

Results: We included 5442 cases of symptoms suspicious of acute cardiac origin (3451 before, 1991 after, 2370 (44%) female, age 55 (SD 19) years). The proportion of patients fulfilling early-rule out criteria decreased from 68% (2348 patients) before to 60% (1195 patients) with the 2015 guidelines ($P < .01$). Those requiring repeated testing significantly ($P < .01$) increased from 22% (743 patients) to 25% (494 patients). Positive results in repeated testing significantly ($P = .02$) decreased from 43% (320 patients) to 37% (181 patients). Invasive diagnostics were performed in 91 patients (2.6%) before and in 75 patients (3.8%) after ($P = .02$) the guideline revision.

Conclusion: The implementation of the more conservative 2015 ESC guidelines led to a minor rise in prolonged observations because of an increase in negative repeated testing and to an increase in invasive procedures.

What's known?

- High sensitive troponin t assays allow the earlier diagnosis of Non-ST-elevation ACS
- This might come at the price of more false positive findings

- The two recent changes in European Society of Cardiology NSTE-ACS guidelines have warranted an increasingly conservative approach warranting more and more tests

What's new?

- Implementation of more conservative guidelines led to a significant increase in repeated testing and a significant decrease in positive results in those tested repeatedly
- Early rule out also decreased significantly, prolonging patients' stay at the ED
- The proportion of those patients going to the cathlab directly from the ED increased from 2.6% to 3.8%

1 | INTRODUCTION

Acute coronary syndrome (ACS) is defined as a condition caused by decreased blood flow in one or more coronary arteries. It leads to decreased function of parts of the myocardium and is an important entity within emergency medicine. ACS is usually classified into ST-segment-elevation myocardial infarction (STEMI) and Non-ST-elevation ACS (NSTE-ACS).[1]

Laboratory testing plays a major role in the further classification of NSTE-ACS into Non-ST elevation myocardial infarction (NSTEMI) and unstable angina pectoris.[2,3] More recently, so called "high-sensitive" troponin T (hsTnT) assays allow an even faster diagnosis of NSTEMI. However, there is also a well-known problem of false-positive (ie, not being caused by acute myocardial ischemia) troponin results. Possible causes are manifold and include renal insufficiency as well as myocarditis, among many others.[4]

Myocardial infarction itself, that is, myocardial injury with clinical evidence of acute myocardial ischaemia, can also be classified according to its cause. "Classical" myocardial infarction, caused by rupture or erosion of a coronary atherosclerotic plaque, is termed type 1 myocardial infarction. A relevant proportion of cases, termed type 2 myocardial infarction, is however caused by a mismatch of oxygen demand and supply for the myocardium. This mismatch might be because of systemic reasons (eg, anaemia or respiratory failure) as well as cardiac reasons, such as tachycardia or arrhythmia. HsTnT as a myocardial, not a coronary, marker does not allow for the differentiation of those two types, nor for proof of a coronary cause.[1]

Various hsTnt cut-offs and measurement strategies have been described and implemented in the past.[5] The guidelines on the management of NSTE-ACS published by the European Society of Cardiology (ESC) since 2015 set a focus on these high sensitive troponin assays.[2] In contrast to previous guidelines, which defined only "negative" (up to the 99th percentile, 30 ng/L for the most common conventional troponin t assays) and "positive" (above this threshold) results, the 2015 ESC guidelines established three different ranges: "rule-out" (up to the 99th percentile, 14 ng/L for the most common high sensitive troponin t assays), "rule-in" (above five-fold of this threshold, ie, usually 70 ng/L), and a "grey area" between those two. Further testing is warranted here 3 hours after the first test. Thygesen et al previously proposed a relative change of 20% from baseline as indicative for acute ischemia.[6] Because of the currently limited number of studies, the cut-off for a "relevant" change in troponin level is still unclear.[2] However, the fact that patients with initially "positive" (ie, above the 99th percentile) results should be treated as "rule-out" if there is only little (ie, within the accuracy of the test) dynamic in repeated testing, while patients with only minor increases should be treated as "rule-in," was hard to comprehend for many clinicians and also induced criticism by laboratory physicians.[7] Tools such as the GRACE score can aid in decision-making, but cannot replace physician judgement.[8]

The 2020 ESC guidelines keep the concept of hsTnt grey areas and warrant an even more conservative approach, that is, emphasizing lower cut-offs for serial measurements.[3] In addition, patients with chest pain of a duration of less than 3 hours might need up to three serial hsTnt measurements within 3 hours after presentation to the ED.[3] This might increase the workload for ED and laboratory personnel, as well as costs.

The impact of the 2020 ESC guidelines on the diagnosis of NSTEMI after widespread clinical implementation is yet unclear. However, the transition to a henceforth more conservative diagnostic approach in patients with short duration of chest pain applies to both guideline changes, the one in 2015 as well as the one in 2020. We therefore chose to use the time point of the implementation of the 2015 guidelines to evaluate the effect of the trend to more conservative hsTnt testing.

Fast and safe diagnosis is crucial for patient safety, whereas quick rule-out is essential to deal with increasing overcrowding of emergency departments. We aimed to assess the impact of the transition to more conservative ESC guidelines on the frequency of early NSTE-ACS rule-out and prolonged observation, as well as repeated and invasive testing at the setting of a high-volume tertiary care emergency department.

2 | MATERIAL AND METHODS

We performed our study at a high-volume, 2200-bed tertiary care university hospital. The emergency department has an approximate turnover of 70 000 patients per year (including approximately 700 patients with acute myocardial infarction) and includes its own intensive (ICU) as well as intermediate care unit with seven positions each. The hospital provides 24 h/7-day coverage for percutaneous transluminal coronary angioplasty. Management of patients with ACS is provided in close collaboration by the departments of emergency medicine and cardiology.

We retrospectively analysed all patients with hsTnt measurements performed for the diagnosis of NSTE-ACS at our department 3 months before (July to September) and 3 months after (October to December) the implementation of the 2020 ERC guidelines for the management of NSTE-ACS.[2] Patients with STEMI were excluded from the analysis. All patients where the treating physician deemed hsTnt measurement to be indicated for the diagnosis of NSTE-ACS were included. This included both patients with chest pain, as well as other angina-like symptoms, such as shortness of breath. The unit of analysis was a single case, that is, one individual patient receiving one or more tests within one in- or outpatient stay at the department.

For hsTnt measurement, the Troponin T hs STAT cobas assay (*Roche Diagnostics Ltd*) was used. Cut-offs were determined according to the ESC guidelines as the 99th percentile of the assay, as well as the five-fold of this percentile.[2,9] Blood sampling was performed directly after admission to the department. Repeated measurements were undertaken if clinically indicated. A 3-hour algorithm for repetitive measurement was used. According to clinical practice, the decision to perform tests was based solely on the discretion of the treating physician in both study periods. According to ESC guidelines, physicians used clinical risk assessment as well as ECG as the basis of their decisions. Figure 1 depicts the 2015 ESC NSTE-ACS algorithm with cut-offs specific to our assay, whereas Figure 2 depicts the 2020 ESC NSTE-ACS algorithm.[2]

Data was extracted from the hospital's digital research, documentation and analysis system. Extracted data included continuous patient identifiers (unique for each patient), admission identifiers (unique for each individual stay of each patient), time-points of laboratory testing, results of hsTnt tests as well as the results of coronary angiography, if performed.

Results were tabulated case-wise. The number of tests per case, absolute and relative dynamics between repeated tests were calculated. Based on these lab-results, cases were classified according to the appropriate guidelines valid at the particular time-point. For cases stretching from the "before"- to the "after"-period, the time-point of the first test was used. We distinguished between:

- Early rule-out (only one test, which fulfilled respective early rule-out criteria)
- Rule-out after repeated testing (multiple tests, the combination of which fulfilled respective rule-out criteria for repeated testing)
- Rule-in after repeated testing (multiple tests, the combination of which fulfilled respective rule-in criteria for repeated testing)
- Immediate rule-in (only one test, which fulfilled respective immediate rule-in criteria)

Absolute and relative frequencies of all these categories as well as for the sum of "rule-in after repeated testing" and "rule-out after repeated testing" were calculated. Mean and standard deviation were calculated for continuous outcomes. Results were tabulated for "before"- and "after"-periods and compared using standard methods (eg, Pearson's χ^2-test), generally regarding a two-sided $P < .05$ as statistically significant.

Absolute and relative frequencies of patients assigned to diagnostic and therapeutic cathlab-procedures were calculated and compared accordingly. The effect of different classification algorithms on clinical outcomes was compared. Microsoft Excel (Microsoft Corp.) and Stata (Stata Corp.) were used for data analysis.

3 | RESULTS

During the study period, a total of 4821 patients (3085 (64%) before, 1430 (46%) female; mean age 56 (20) years; 1736 (36%) after, 940

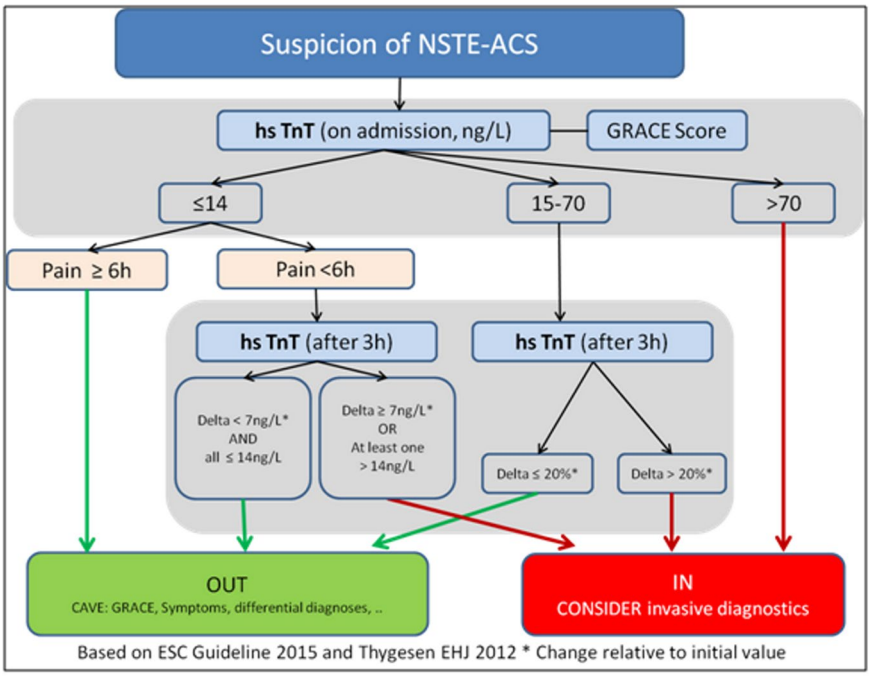

FIGURE 1 2015 Diagnostic pathway for NSTE-ACS

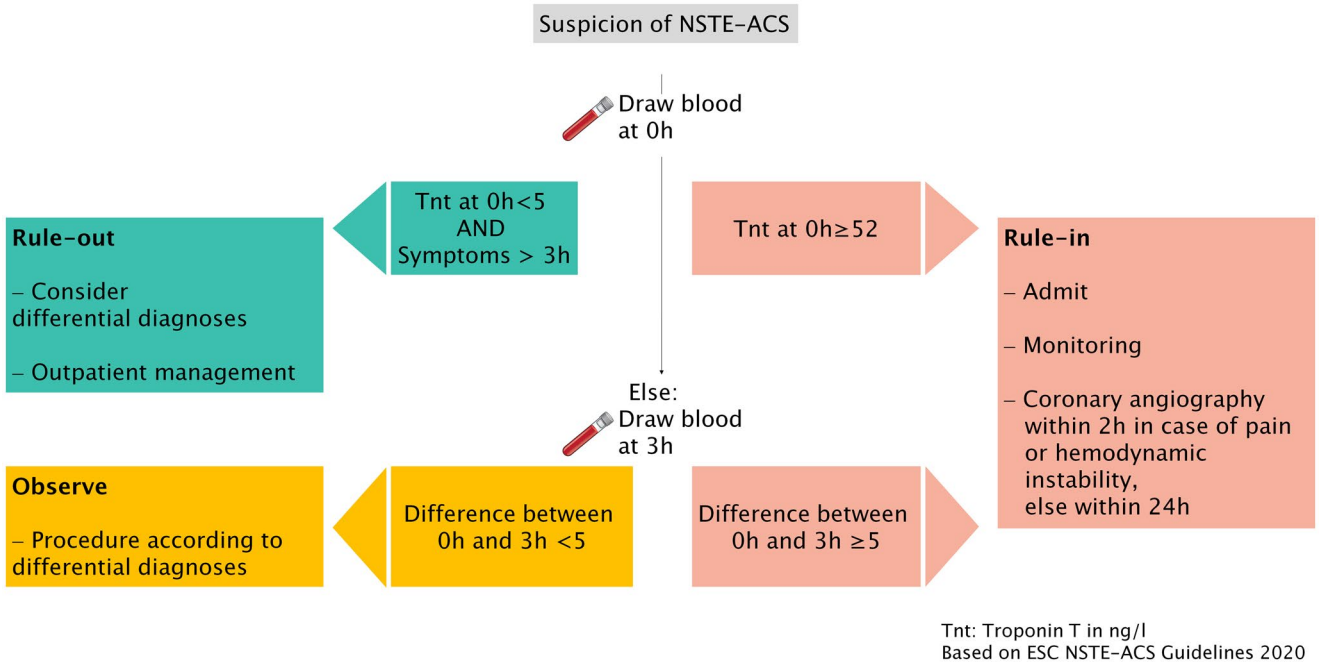

FIGURE 2 2020 Diagnostic pathway for NSTE-ACS

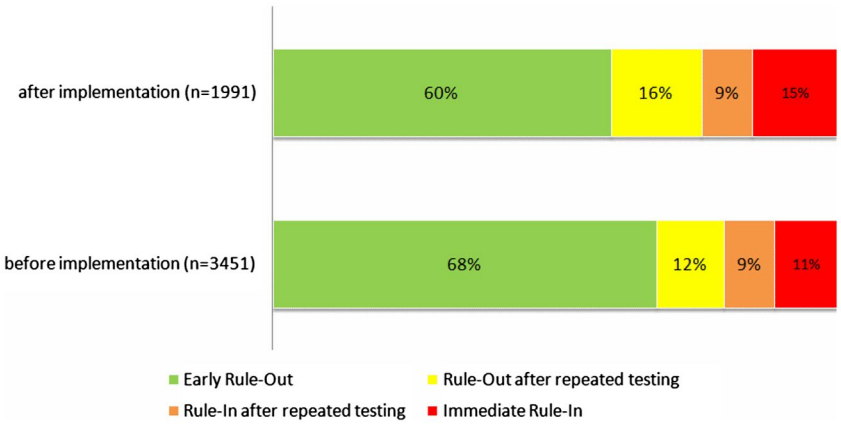

FIGURE 3 Main results

(54%) female, mean age 52 (19) years) amounting to 5442 cases including patients being seen multiple times (3451 before, 1991 after) with symptoms suspicious of acute cardiac origin but not STEMI were treated at the department. At the same time, total number of ED visits were 21 132 before, and 16 421 after.

The proportion of cases fulfilling early rule-out criteria decreased from 68% (2348 cases) before to 60% (1195 cases) after implementation of the new guidelines ($P < .01$). The proportion of cases who required repeated testing increased significantly from 22% (743 cases) to 25% (494 cases; $P < .01$), whereas the proportion of positive results in repeated testing decreased significantly from 43% (320 cases) to 37% (181 cases; $P = .02$) of those undergoing such repeated testing. Together with those immediately ruled in, this means that over the whole study period, in a total of 1163 cases (21% of overall cases) a diagnosis of ACS was made (in 19% of patients before, and 24% of patients after). See Figure 3 for a graphical depiction and Table 1 for demographic details of respective groups.

Immediate invasive diagnostics (coronary angiography) were performed in 91 patients (2.6%) before and in 75 patients (3.8%) after implementation of new guidelines ($P = .02$). This difference is explained by the individual patients' risk factors and symptoms. Low risk NSTE-ACS-patients can wait up to 24 hours for PCI according to ECS-guidelines.[2]

Regarding PCI-findings, the infarct-related artery (IRA) was identified in 37 patients (26 LAD, 1 CX, 7 RCA, 1 LM) before (19 single-, 1 double-, 17 triple-vessel disease) and in 52 patients (23 LAD, 12 CX, 15 RCA, 1 LM, 1 unclear) after the cut-off change (5 single-, 5 double-, 42 triple-vessel disease) ($P = .01$) (Table 2).

During their entire stay at the hospital, a total of 169 patients (24.9%) before and 128 patients (26.5%) after underwent

TABLE 1 Main results

	Before implementation of new guidelines n = 3451 (63%)				After implementation of new guidelines n = 1991 (37%)			
N = 5442 (100%)	Early rule out	Rule-out after repeated testing	Rule-in after repeated testing	Immediate rule-in	Early rule out	Rule-out after repeated testing	Rule-in after repeated testing	Immediate rule-in
Total, n (%)	2348 (68)	423 (12)	320 (9)	360 (10)	1195 (60)	313 (16)	181 (9)	302 (15)
Female, n (%)	1001 (43)	182 (43)	135 (42)	112 (31)	620 (52)	135 (43)	76 (42)	109 (36)
Mean age, y (SD)	54 (20)	59 (16)	63 (16)	66 (16)	47 (17)	64 (18)	62 (16)	61 (18)

Abbreviation: SD, standard deviation.

coronary angiography, 106 and 81 of them, respectively, also receiving interventions.

4 | DISCUSSION

Quick decision making is a cornerstone of emergency medicine. Aside contributing to patient safety, it helps to avoid ED-overcrowding, which is a known factor to negatively influence the quality of care and increases the likelihood of patients leaving without being seen.[10-13]

In patients with NSTE-ACS, laboratory testing is necessary for diagnosis. Current guidelines account for the modern assays' ability to identify even minimal increases in troponin-levels. Nevertheless, this advantage must be counter-balanced with expenditure in cost and time spent because of multiple testing, necessitated by false-positive results. As cut-offs for repetitive testing are lower in the 2020 ESC guidelines, this might result in extensive retesting. In addition, the 2015 guidelines limited serial hsTnt measurements to a maximum of two time points, while the 2020 version warrants blood sampling at up to 3 points in time.[2,3]

The fact that only 21% of all cases, which underwent troponin t testing, finally resulted in a diagnosis of ACS, underline a rather unselective use of this laboratory test. This is consistent with prior research which indicates that clinicians' threshold to perform troponin tests varies widely.[14] The emergency department, where time is precious and rather little is known about a patient's history and baseline condition considerably differs from an inpatient ward of a cardiology department. Recent developments in guidelines stress the importance of scores as well as different degrees of ECG-changes to help with those decisions, but ultimately cannot replace physician assessment.[3,8]

Our findings indicate a minor rise in prolonged observation, mainly explained by an increase in eventually negative repeated hsTnt-testing from 12% of cases before, to 16% after. These 4% equal to 80 to 138 patients in our study groups. In our setting, an additional 100 hsTnt-tests would cost around 3400 Euro (at a cost of 34.31 Euro per test at our hospital), not including cost of staff time. These costs are representative of the health care system in our country, but could differ vastly in other countries and systems. The increased rate of positive test results also leads, as initially suspected, to more invasive procedures, therewith possibly incrementing complications. Naturally, if indicated, those invasive procedures form a cornerstone of the treatment of coronary heart disease, increasing long-term survival and symptom control.[2,3]

Nevertheless, still only around 1 in 4 patients finally classified as "rule-in" underwent coronary angiography during their stay at the hospital. In a large proportion of patients, further cardiological evaluation hence deems troponin elevation to be either caused by type II myocardial infarction (ie, more because of systemic causes than to acute coronary plaque rupture), or coronary angiography and PCI not to be beneficial for these patients.

TABLE 2 infarct-related arteries (IRA) and types of vessel disease

IRA and type of vessel disease N = 89 (100%)	Before implementation of new guidelines n = 37 (42%)	After implementation of new guidelines n = 52 (58%)
Left anterior descending coronary artery, n (%)	26 (70)	23 (44)
Right coronary artery, n (%)	7 (19)	15 (29)
Circumflex artery, n (%)	1 (3)	12 (23)
Left main, n (%)	1 (3)	1 (2)
Unclear, n (%)	0 (0)	1 (2)
Single vessel disease, n (%)	19 (51)	5 (10)
Double vessel disease, n (%)	1 (3)	5 (10)
Triple vessel disease, n (%)	17 (46)	42 (81)

Abbreviation: IRA, Infarct-related artery.

Divergent intervals for repeated measurement of troponin-levels were and are still recommended throughout the literature.[15,16] At our department, we use the 0/3 hour-algorithm. A study investigating the 0/1 hour-algorithm found that those in need of repeated testing are mostly elderly and multimorbid patients.[17] Both are populations we frequently encounter at our department. The impact of older and newer troponin essays was not evaluated in that study. Another trial aimed to investigate differences between a 0/3- and a 0/1-hsTnt-algorithm and found comparable performance. Noteworthy, the onset of chest pain was significantly different between the study groups.[18] Our results did not include a 0/1 hour-algortithm, warranting future research.

An important point is the type of troponin analysed, which is troponin T or I in most places. A large study showed similar safety properties for these assays when used in a 0/3-hour setting.[19]

The total number of patients with ACS seen patients in the before- and after-groups of our study differed notably. We have no definite reasons for this, as no further structural changes besides those studied were implemented at our department at that time point. There were also no relevant differences in patients' demographics between the two periods. Variations in total ED visits party, but not totally explain the differences: The total number of visits to the ED in the "after"-period was 78% of that in the "before"-period (21 132 before, and 16 421 after). The number of visits because of symptoms suspicious of acute cardiac origin in the "after" period was however only 58% of that before (3451 before, 1991 after). Seasonal variations (the "before" period took place from July to September, whereas the "after" period took place from October to December) in the incidence of acute cardiovascular disease have, however, been observed before.[20]

We did not intend to evaluate the validity of the 2015 or 2020 ESC-guidelines, the 0/3 hour algorithm or the cut-offs for our troponin essays, which has already been done multiple times. Instead, we aimed to evaluate the consequences of the implementation of a guideline change to a more conservative approach indicating repeated testing in a real-world setting. Notably, repeated testing was not harmful or useless in all patients, in whom ACS could finally be ruled out. Plentiful differential diagnoses are associated with elevated troponin levels, such as chronic renal failure or pre-existing cardiomyopathy.

Finally, it has been shown that cardiac biomarkers are especially frequently ordered in patients without symptoms suggestive of ongoing ischemia.[21] Unfortunately, this vulnerable population has at the same time an increased risk for elevated troponin levels without an acute cause.[22] For these reasons, a thorough medical assessment should forego every measurement of troponin levels.

5 | CONCLUSIONS

In our high-volume, real-world setting, the implementation of the more conservative ESC guidelines led to a minor rise in prolonged observation, mainly explained by an increase in eventually negative repeated high sensitive troponin t-testing. This corresponds to slightly prolonged duration of stay at the emergency department and higher costs per patient, as well as a slight increase in invasive testing.

AUTHORS CONTRIBUTIONS

CK developed the design of the study, participated in data collection, planned and performed data analysis, drafted the article. VF participated in the design of the study, participated in data collection and analysis, and critically revised the article. RT participated in the design of the study, participated in data collection and analysis, and critically revised the article. CH participated in the design of the study, participated in data collection and analysis, and critically revised the article. WS participated in the design of the study, participated in and supervised data analysis, critically revised the article, and supervised the whole project. SR participated in the design of the study, participated in data collection and analysis, and critically revised the article. TW participated in the design of the study, participated in data collection and analysis, and critically revised the article. HH participated in the design of the study, participated in data collection and analysis, and participated in the drafting of the article.

AL participated in the design of the study, participated in data collection and analysis, and critically revised the article. DR participated in the design of the study, participated in and supervised data analysis, participated in the drafting of the article, and supervised the whole project. All authors read and approved the final version of the article.

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