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Diagnostic and Cost Efficiency of the 0-h/1-h Rule-out and Rule-in Algorithm for Patients With Chest Pain in the Emergency Department

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Background: This study investigated the economic impact of the European Society of Cardiology (ESC) clinical practice guideline recommendation of using the 0-h/1-h rule-out and rule-in algorithm with high-sensitivity cardiac troponin assays (0/1-h algorithm) to triage patients presenting with chest pain.

Methods and Results: This post hoc cost-effectiveness evaluation (DROP-ACS; UMIN000030668) used deidentified electronic medical records from health insurance claims from 2 diagnostic centers in Japan. A cost-effectiveness analysis was conducted with 472 patients with care provided following the 0/1-h algorithm (Hospital A) and 427 patients following point-of-care testing (Hospital B). The clinical outcome of interest was all-cause mortality or subsequent myocardial infarction within 30 days of the index presentation. The sensitivity and specificity for the clinical outcome were 100% (95% confidence interval [CI] 91.1–100%) and 95.0% (95% CI 94.3–95.0%), respectively, in Hospital A and 92.9% (95% CI 69.6–98.7%) and 89.8% (95% CI 89.0–90.0%), respectively, in Hospital B. If the diagnostic accuracy of the 0/1-h algorithm was implemented in Hospital B, it is expected that the number of urgent (<24-h) coronary angiograms would decrease by 50%. Incorporating this assumption, implementing the 0/1-h algorithm could potentially reduce medical costs by JPY4,033,874 (95% CI JPY3,440,346–4,627,402) in Hospital B (JPY9,447 per patient; 95% CI JPY 8,057–10,837 per patient).

Conclusions: The ESC 0/1-h algorithm was efficient for risk stratification and for reducing medical costs.

Key Words: 0/1-h algorithm; Acute coronary syndrome; High-sensitivity troponin T; Medical costs

Emergency department (ED) crowding has become a barrier to timely and efficient care in recent decades.[1,2] Patients with non-ST elevation acute coronary syndrome (NSTE-ACS) require an efficient triage system.[3,4] Approximately 2–5% of patients with NSTE-ACS who are discharged home often have poor outcomes, resulting in a high rate of malpractice suits in emergency medicine. Meanwhile, more than half of ED patients with chest pain have clinical findings consistent with NSTE-ACS after the initial evaluation and are admitted to hospital. Approximately half of these patients, after evaluation in hospital, do not have NSTE-ACS. In the US, these negative inpatient cardiac evaluations cost approximately US$6 billion each year.[5,6] Decision analytic models have suggested that the use of the high-sensitivity cardiac troponin test (hs-cTnT) can be generally cost-effective for NSTE-ACS. Moreover, hs-cTnT-guided diagnostic strategies reduce the use of stress testing by nearly one-third. Non-adherence to management recommendations significantly affects the potential for cost savings.[7] American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA), European Society of Cardiology (ESC), and Japanese Cardiology Society (JCS) clinical practice guidelines recommend serial hs-cTnT measurements for the diagnosis of NSTE-ACS through repeat samplings at 1, 2, and 3 h after arrival at the ED, observing the pattern of increase or decrease, as well as the repeated value itself, based on assay-specific diagnostic thresholds.[8–10] The International Federation of Clinical Chemistry Committee on Clinical Applications of Cardiac Bio-Markers provides educational material about cardiac biomarkers, emphasizing hs-cTnT assays.[11,12] The method of risk stratification by troponin values measured at the time of admission and 1 h later is called the 0-h/1-h rule-out

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and rule-in algorithm with high-sensitivity cardiac troponin assays (0/1-h algorithm), and the ESC guideline indicates that this algorithm can be used for the triage of patients presenting with chest pain as class I.[9] However, current JCS guidelines only allow the use of qualitative measurements of cardiac troponin (i.e., point-of-care testing [POCT]), in which case retesting will be performed 6 h after symptom onset.[10] Several types of POCT to measure cardiac troponin are used in clinical practice because they require only 15–20 min to obtain results.[13–15] The problem with POCT is the high rate of false positives, leading to unnecessary hospitalizations and higher costs, without a reduction in clinical events.[16–18]

The aims of this study were to compare the diagnostic efficiency for NSTE-ACS between one hospital implementing the 0/1-h algorithm using hs-cTnT (Hospital A) and another hospital applying POCT (Hospital B) and to evaluate the potential cost saving of the 0/1-h algorithm. For the subsequent simulation analysis to evaluate cost savings, we made the assumption that Hospital B used the 0/1-h algorithm with the hs-cTnT assays.

Methods

Study Design and Data Source

The Diagnostics and Reduction of Asian Patients with ACS Cost Analysis Based on the 0/1-h Algorithm Using High-sensitivity Cardiac Troponin study (DROP-ACS; UMIN000030668) is an international multicenter diagnostic hospital investigation conducted at 5 sites in 2 countries (Japan and Taiwan) and has been described in detail elsewhere.[19,20] Briefly, the participants of DROP-ACS were adults (aged 30–89 years) presenting to the ED with suspected NSTE-ACS. Implementation of the 0/1-h algorithm using hs-cTnT (Cobas; Roche Diagnostics, Indianapolis, IN, USA; **Supplementary Figure**) was according to the discretion of attending physicians. The exclusion criteria were as follows: ST-elevation myocardial infarction (STEMI); chronic kidney disease (serum creatinine >3 mg/dL); congestive heart failure, defined as the presence of hypoxia and typical pulmonary congestion confirmed on a chest radiograph; ventricular tachycardia; and ED arrival >24 h after the onset of symptoms. The ACC/AHA guidelines emphasize eliminating testing for which evidence is lacking and reducing the testing of low-risk patients for whom testing deferral is appropriate.[21] Therefore, we excluded patients who were hospitalized but had not undergone a cardiac examination (including coronary angiography [CAG], coronary computed tomography angiography [CTA], or stress electrocardiography [ECG]) because they were not considered suspect for coronary artery disease in this retrospective analysis.

Given that the inclusion and exclusion criteria of DROP-ACS and the standard operating procedures at the participating hospitals remained unchanged over the entire study period, we had an opportunity to compare data from patients evaluated with the hs-cTnT assay (Hospital A) with that from comparable patients assessed with POCT (AQT90 FLEX cTnT; limit of detection 15.4 ng/L; 99th percentile: 17 ng/L) as customary practice[13] (Hospital B). An attending physician in Hospital B masked the results of the hs-cTnT data. Both hospitals were tertiary university hospitals in urban areas. Because a randomized controlled trial using both methods simultaneously in the same institution is not feasible, this methodology could be considered the best possible alternative.

We recruited consecutive patients (n=608 in Hospital A and n=603 in Hospital B) with suspected NSTE-ACS from each hospital over the same period. The study used deidentified data from health claims and the Diagnosis Procedure Combination (DPC; the flat-fee payment system) from hospitals in Japan, obtained from the Medical Data Vision Co. Ltd (Tokyo, Japan), reporting in Japanese yen (JPY). This database comprised inpatient and outpatient medical claims data from hospitals. To assess the medical costs of patients presenting with chest pain, those who did not undergo heart disease examinations (including CAG, coronary CTA, or stress ECG during hospitalization) were excluded from the analysis because they were not considered to have cardiac disease-related disease.

The study was approved by the ethics committees of the participating hospitals and was conducted in accordance with the Helsinki Declaration of 1971, as revised in 1982.

Follow-up and Clinical Endpoints

Patients were contacted 30 days after the index visit. The endpoints of this study were major adverse cardiovascular events (MACE), including cardiac death and subsequent NSTE-ACS, during the 30-day follow-up after the index visit. NSTE-ACS comprised acute myocardial infarction and unstable angina, which were defined according to the Fourth Universal Definition of Myocardial Infarction. This required evidence of myocardial necrosis in addition to ischemia.[22] For follow-up, patients were examined by cardiologists at the same hospital. If the physicians were unavailable, we tracked patients via hospital records and conducted a telephone follow-up to determine adverse events 30 days from their initial presentation.

Cost Estimation

All Japanese citizens are covered by social health insurance according to their employment or residence. Japan has reduced inequities between the different insurance plans by making co-payment rates uniform, except for older people and children, and by mandating cross-subsidization between plans to account for different proportions of enrolled older individuals. This healthcare system made a synergistic contribution by ensuring access to healthcare for all citizens and by regulating prices so that out-of-pocket payments were low.[23]

Using claims data, we evaluated the total costs for both inpatient and outpatient care in the department of cardiology for 30 days after the index presentation. The claim data component corresponded to the "hospital fee", which included the basic hospital charge, pharmaceuticals, injections, laboratory examinations, and other related expenses, paid on a per-day payment scheme. The fee-for-service (FFS) component corresponded to charges for CAG and other related expenses. Revenue equals the sum of the FFS components. For patients who underwent urgent CAG, we estimated the cost up to the day after the procedure. These patients were defined as those undergoing CAG within 24 h after admission. We did not include fees for material costs related to percutaneous coronary intervention (PCI) procedures because this study aimed to determine the cost of diagnosis, not the cost of treatment.

The total hospitalization costs were calculated as the sum of bundled payments and the FFS without the food fee. The bundled payment for each hospitalization was calculated according to the codes in the International Classification

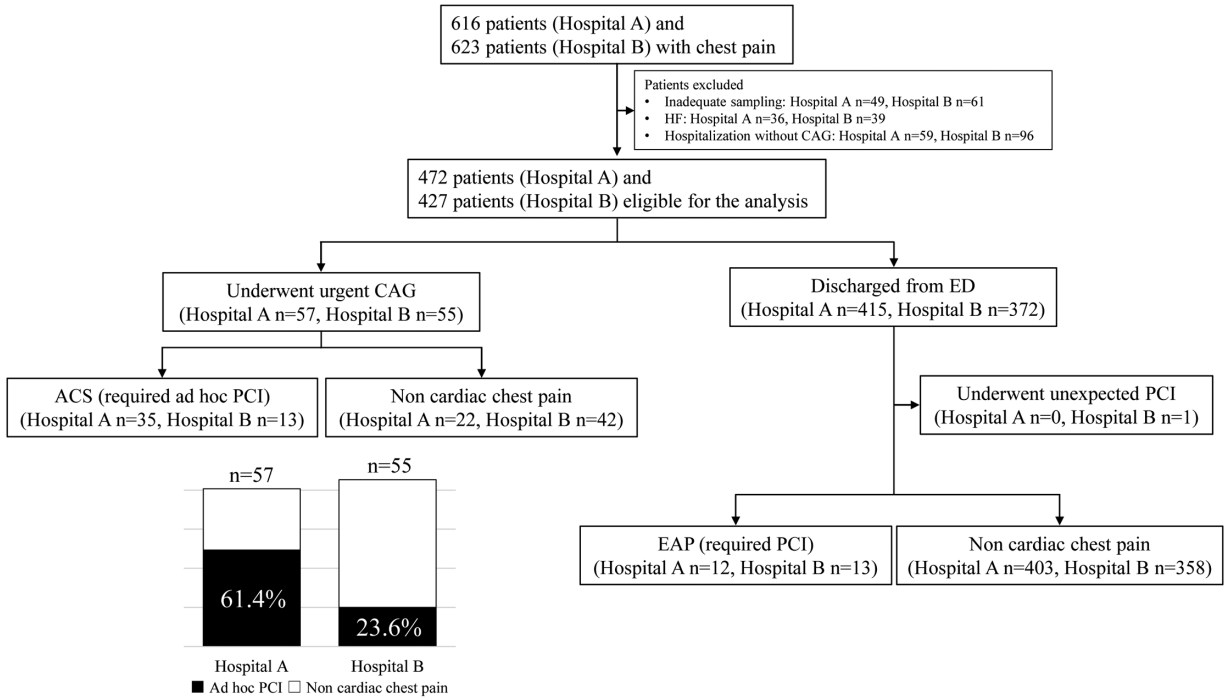

Figure 1. Study flowchart. ACS, acute coronary syndrome; CAG, coronary angiography; EAP, effort angina pectoris; ED, emergency department; HF, heart failure; PCI, percutaneous coronary intervention.

of Diseases 10th revision and the coefficient for each facility. The costs were set as follows:

- CAG, defined as "tests using the cardiac catheter method in diagnostic angiography (D206)": cost JPY40,000
- elective PCI, that is, "percutaneous coronary intervention for coronary artery disease without acute myocardial infarction or unstable angina pectoris (K549)": cost JPY216,800
- urgent PCI, that is, "percutaneous coronary intervention for coronary artery disease with acute myocardial infarction (K549)": cost JPY343,800
- stress ECG, that is, "stress cardiogram (D209)": cost JPY3,800
- coronary CTA: cost JPY21,200 (JPY11,000 for coronary CTA was added to the "CT imaging [E200]" cost of JPY10,200)
- stress scintigrams: cost JPY84,120 (JPY9,000 for stress scintigrams was added to the "scintigram [E100]" cost of JPY75,120).

The data were anonymized and did not include any information that could be used to identify individuals or hospitals. Each patient was given a hospital-specific identifier, and all patients were regarded as a single individual, regardless of the combination of inpatient and outpatient data. The DPC data used for billing included patient demographics and clinical information, admission and discharge statuses, diagnoses, surgeries and procedures performed, medications, and special reimbursements for specific conditions.

Sensitivity Analysis

One-way sensitivity analyses were conducted to assess the impact of each parameter on the results. The sensitivity, specificity, cost, and prevalence rate of NSTE-ACS parameters used in the analyses were varied for each calculation within the 95% confidence interval (CI) range.

Statistical Analysis

Continuous variables are presented as the mean (±SD) or as the median with interquartile range (IQR); categorical variables are presented as numbers and percentages. Based on their distribution, continuous variables were compared using one-way analysis of variance for 3-group comparisons. The sensitivity and negative predictive value for MACE in the rule-out group and the specificity and positive predictive value for MACE in the rule-in group were calculated. All statistical analyses were performed using SPSS (version 16.0; IBM Corp., Armonk, NY, USA), R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria), and JMP version 9.0.0 (SAS Institute Inc., Cary, NC, USA). One author (K.I.) had full access to all study data and assumed full responsibility for its integrity and data analysis.

Results

Patient Characteristics

Overall, 616 patients in Hospital A and 623 patients in Hospital B were enrolled in the study (**Figure 1**). Of these patients, 85 from Hospital A and 100 from Hospital B with STEMI, cardiopulmonary arrest, and heart failure were excluded because troponin measurement was unnecessary for the diagnosis of these conditions. Ultimately, we evaluated 472 patients in Hospital A and 427 patients in

Table 1. Summary Statistics

Statistics	ACS	No ACS
Hospital A		
Urgent CAG (n)	35	22
Rule-out (hs-cTnT assay) (n)	0	415
Sensitivity (%) (95% CI)	100 (91.1–100)	
Specificity (%) (95% CI)	95.0 (94.3–95.0)	
Prevalence rates of ACS (%) (95% CI)	7.4 (5.9–8.9)	
Hospital B		
Urgent CAG (n)	13	42
Rule-out (POCT) (n)	1	371
Sensitivity (%) (95% CI)	92.9 (69.6–98.7)	
Specificity (%) (95% CI)	89.8 (89.0–90.0)	
Prevalence rates of ACS (%) (95% CI)	3.3 (2.6–3.9)	

ACS, acute coronary syndrome; CAG, coronary angiography; CI, confidence interval; hs-cTnT, high-sensitivity cardiac troponin T; POCT, point of care testing.

Table 2. Simulation Analysis

	Prior to simulation analysis (n)	Post-simulation analysis (n)	Delta values (n)	Cost-effectiveness (JPY)
Urgent CAG	42	21	−21	−5,944,985
Unexpected PCI	1	0	−1	−722,279
Discharge from ED	371	392	+21	1,960,753
Ad hoc PCI	13	14	+1	672,636
Total	427	427	0	−4,033,874

CAG, coronary angiography; ED, emergency department; JPY, Japanese yen; PCI, percutaneous coronary intervention.

Hospital B. The median age of patients in Hospital A was higher than that of patients in Hospital B (72 years [IQR 60–82 years] vs. 68 years [IQR 55–76 years], respectively; P<0.05). There was no difference in sex distribution between Hospitals A and B (59.5% vs. 59.3% male, respectively; P=0.9). The prevalence of NSTE-ACS was 7.4% and 3.3% in Hospitals A and B, respectively. Hospital A provided medical care according to the 0/1-h algorithm. However, there were relatively more older men in the rule-in group; therefore, the risk score in this group was also higher than that in the rule-out group (**Supplementary Table**).

Clinical Care

Overall, 57 (12.1%) patients in Hospital A and 55 (12.9%) patients in Hospital B required urgent CAG, with ad hoc PCI in 35 (61.4%) patients and 13 (23.6%) patients, respectively (**Figure 1**). A total of 415 patients in Hospital A and 372 patients in Hospital B patients were discharged from the ED, and none of the patients in Hospital A and 1 patient in Hospital B experienced subsequent NSTE-ACS during the 30-day follow-up period. Among the patients discharged from the ED in Hospitals A and B, we observed low overall rates of utilization of CAG (1.9% and 6.3%, respectively), non-invasive functional tests (i.e., stress ECG; 11.6% and 9.8%, respectively), and coronary CTA (3.6% and 1.2%, respectively); there were no significant differences between the 2 hospitals. Only 12 (2.5%) patients in Hospital A and 13 (3.0%) patients in Hospital B required staged PCI during the 30-day follow-up period. Thus, 403 (85.4%) patients in Hospital A and 358 (83.8%) patients in Hospital B did not require revascularization during the 30-day follow-up period from the index visit (the final diagnosis was non-cardiac chest pain). From these results, the sensitivity and specificity for NSTE-ACS were 100% (95% CI 91.1–100%) and 95% (95% CI 94.3–95.0%), respectively, for Hospital A and 92.9% (95% CI 69.6–98.7%) and 89.8% (95% CI 89.0–90.0%), respectively, for Hospital B (**Table 1**).

Scenario Analysis

To simulate a situation in which Hospital B implemented the 0/1-h algorithm, we replaced the values of sensitivity and specificity of Hospital B with those of Hospital A (**Table 2**). The number of patients undergoing urgent CAG without PCI decreased from 42 to 21, and the number of patients not undergoing urgent CAG and discharged from the ED increased from 371 to 392. As a result, urgent CAG decreased by 21 patients and unexpected PCI decreased by 1 patient, yielding cost reductions of JPY5,944,985 and JPY722,279, respectively. In addition, 21 more patients were discharged from the ED, and the ad hoc PCI increased by 1 patient, who was found with subsequent NSTE-ACS in Hospital B, yielding cost increases of JPY1,960,753 and JPY672,636, respectively. Thus, a total of JPY4,033,874 would have been saved in medical expenses. The results of the 1-way deterministic sensitivity analysis with the tornado diagram for the implementation of the sensitivity and specificity of Hospital A for Hospital B are shown in **Figure 2** and **Table 3**. This sensitivity analysis recalculated the net costs of care using the 0/1-h algorithm vs. POCT, varying 1 variable at a time within the model. The value of

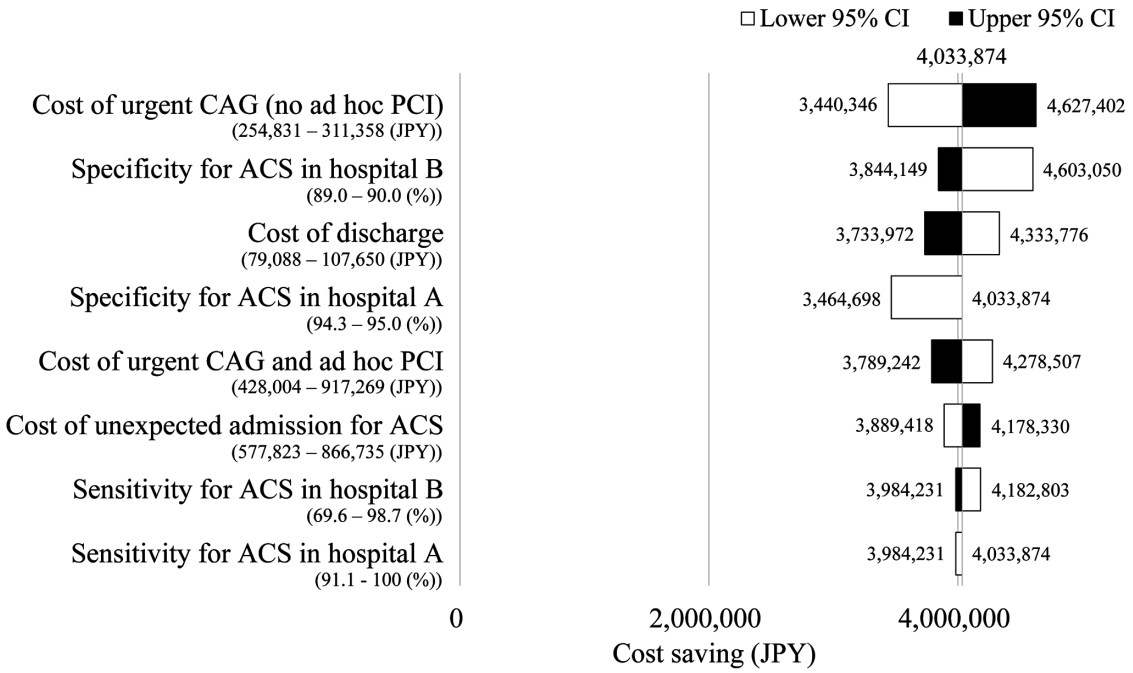

Figure 2. Univariate sensitivity analysis of the high-sensitivity system vs. the point-of-care testing (POCT) system. The sensitivity analysis recalculates the net expected cost of each strategy (0/1-h algorithm vs. typical care), varying 1 model input at a time to its high and low values relative to its baseline value. In this simulation, the cost of the 0/1-h algorithm remains lower for each scenario evaluated on sensitivity analysis, and the results are most sensitive to the cost of coronary angiography (CAG) without acute coronary syndrome (ACS), the cost of no CAG without ACS, and the specificity of Hospital B and Hospital A. CI, confidence interval; JPY, Japanese yen; PCI, percutaneous coronary intervention.

Table 3. Model Input Values for Simulations

Model input	Baseline value	95% CI
Cost of urgent CAG (no ad hoc PCI) (JPY)	283,095	254,831–311,358
Specificity for ACS in Hospital B (%)	89.8	89.0–90.0
Cost of discharge (JPY)	93,369	79,088–107,650
Specificity for ACS in Hospital A (%)	95.0	94.3–95.0
Cost of urgent CAG and ad hoc PCI (JPY)	672,636	428,004–917,269
Sensitivity for ACS in Hospital B (%)	92.9	69.6–98.7
Cost of unexpected admission for ACS (JPY)	722,279	577,823–866,735
Sensitivity for ACS in Hospital A (%)	100	91.1–100

Abbreviations as in Tables 1,2.

a given variable was adjusted to high and low values relative to the baseline. One-way sensitivity analysis revealed that the cost of urgent CAG without ad hoc PCI had the greatest effect on the results (from JPY3,440,346 to JPY 4,627,402). Interestingly, the specificity for NSTE-ACS in Hospital B was 89.8% (95% CI 89.0–90.0%); thus, only a 1% difference would reflect a greater range of medical cost reduction (from JPY3,844,149 to JPY4,603,050). Conversely, the sensitivity for NSTE-ACS in Hospital B was 92.9% (95% CI 69.6–98.7%), a 29.1% larger difference. However, the medical cost reduction was smaller, with a range of JPY3,984,231–4,182,803. Collectively, higher specificity is preferable over higher sensitivity with respect to medical cost reductions.

Discussion

This study evaluated the cost-effectiveness of diagnostic approaches to NSTE-ACS by comparing the routine clinical application of the ESC 0/1-h algorithm with a POCT method for unselected patients presenting to the ED with acute chest discomfort suspected to be NSTE-ACS. To the best of our knowledge, this is the first study to complete such a detailed assessment using the contemporary Japanese reimbursement system. We report 3 main findings. First, implementation of the 0/1-h algorithm reduced unnecessary urgent hospitalization and catheterization, and thus reduced medical costs. Second, the sensitivity and specificity of the 0/1-h algorithm for NSTE-ACS were better than those of

POCT. Third, there were no significant differences in non-invasive test rates after discharge from the ED. By switching from POCT to the 0/1-h algorithm, medical costs would decrease by JPY4,033,874 per 427 patients (approximately JPY10,000 per patient) according to our findings. On sensitivity analysis, the result of the base-case analysis (cost-saving expected by using the 0/1-h algorithm) was not reversed in all parameters, confirming robustness. Avoiding unnecessary admissions for urgent CAG had the greatest effect on reducing medical costs. Therefore, improvements in specificity yielded greater cost-effectiveness than those in sensitivity.

Several observational studies on the introduction of an hs-cTnT assay have shown positive results with potential reduction of medical costs.[24–26] Ambavane et al reported that the implementation of the 0/1-h algorithm would better reduce the medical costs than would standard care.[27] That study was based on the assumption that the algorithm was applied absolutely and projected the potential cost saving.[27] Conversely, Chuang et al compared costs between the 0/1-h and 0/3-h algorithms based on the randomized controlled RAPID-TnT trial database and found no significant difference in total cost or adverse clinical outcomes between the 2 algorithms.[28] The higher subsequent unplanned inpatient stay was considered to cause the increase in the cost in 0/1-h algorithm arm.[28] However, because the comparison was made when the follow-up period was extended to 1 year, there is a possibility that various factors may have been affected during the course of the study.

POCT systems are easy to use in the ED and enable quick decisions.[14] However, because their diagnostic efficiency is slightly lower than that of the highly sensitive measurement system, over-triage tends to occur. In the present study, only 1 case was overlooked for NSTE-ACS. Thus, it is preferable to use a highly sensitive measurement system as much as possible to save medical resources until diagnostic efficiency is improved in a POCT system.[29]

The difference in the medical costs between the 2 hospitals can be attributed to the differences in specificity for NSTE-ACS diagnosis. That is, from the perspective of the specificity for the diagnosis of NSTE-ACS, there is no difference in medical cost because both hospitals provided sufficient medical care to ensure few misdiagnoses of NSTE-ACS (Hospital A, none; Hospital B, only one). However, the POCT protocol implemented in Hospital B resulted in more hospitalizations and thus higher medical costs. Sensitivity analyses showed that the implementation of the 0/1-h algorithm did not further decrease medical costs even if patients were not hospitalized. Conversely, increasing hospitalizations would be considered over-triage and would result in increasing medical costs. In particular, increasing the specificity of NSTE-ACS diagnosis does not significantly reduce medical costs; however, decreasing the sensitivity would result in the increase of medical costs.

This study has some limitations. First, we conducted a simulation analysis that applied the results obtained at one facility to another and compared a small number of hospitals. However, the sensitivity and specificity of the 0/1-h algorithm are similar to those reported previously.[30] Thus, we believe that the cost reduction effect can be generalized, although validation studies are needed. Second, findings from the cost analyses per se are not necessarily generalizable to healthcare systems other than those observed in this trial because of potential cost differences. Third, we cannot comment on the utility of the ESC 0/1-h algorithm in patients with end-stage renal failure on chronic dialysis because these patients were excluded from the initial studies that derived and validated this algorithm.

Conclusions

The ESC 0/1-h algorithm using hs-cTnT based on assay-specific diagnostic thresholds had better diagnostic ability than POCT, and its use appears to be cost-effective.

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IRB Information

This study was approved by the Ethical Review Board of Juntendo University Nerima Hospital (Reference no. 17-16).

Data Availability

All deidentified participant data will be shared upon request, ending 10 years after the publication of this article, and for any kind of analyses. The data will be shared as Excel files via email. Please contact the corresponding author directly to request data sharing.

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Supplementary Files

Please find supplementary file(s);
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