



0/1-Hour Triage Algorithm for Myocardial Infarction in Patients With Renal Dysfunction

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et al

BACKGROUND: The European Society of Cardiology recommends a 0/1-hour algorithm for rapid rule-out and rule-in of non-ST-segment elevation myocardial infarction using high-sensitivity cardiac troponin (hs-cTn) concentrations irrespective of renal function. Because patients with renal dysfunction (RD) frequently present with increased hs-cTn concentrations even in the absence of non-ST-segment elevation myocardial infarction, concern has been raised regarding the performance of the 0/1-hour algorithm in RD.

METHODS: In a prospective multicenter diagnostic study enrolling unselected patients presenting with suspected non-ST-segment elevation myocardial infarction to the emergency department, we assessed the diagnostic performance of the European Society of Cardiology 0/1-hour algorithm using hs-cTnT and hs-cTnI in patients with RD, defined as an estimated glomerular filtration rate <60 mL/min/1.73 m², and compared it to patients with normal renal function. The final diagnosis was centrally adjudicated by 2 independent cardiologists using all available information, including cardiac imaging. Safety was quantified as sensitivity in the rule-out zone, accuracy as the specificity in the rule-in zone, and efficacy as the proportion of the overall cohort assigned to either rule-out or rule-in based on the 0- and 1-hour sample.

RESULTS: Among 3254 patients, RD was present in 487 patients (15%). The prevalence of non-ST-segment elevation myocardial infarction was substantially higher in patients with RD compared with patients with normal renal function (31% versus 13%, $P<0.001$). Using hs-cTnT, patients with RD had comparable sensitivity of rule-out (100.0% [95% confidence interval {CI}, 97.6–100.0] versus 99.2% [95% CI, 97.6–99.8]; $P=0.559$), lower specificity of rule-in (88.7% [95% CI, 84.8–91.9] versus 96.5% [95% CI, 95.7–97.2]; $P<0.001$), and lower overall efficacy (51% versus 81%, $P<0.001$), mainly driven by a much lower percentage of patients eligible for rule-out (18% versus 68%, $P<0.001$) compared with patients with normal renal function. Using hs-cTnI, patients with RD had comparable sensitivity of rule-out (98.6% [95% CI, 95.0–99.8] versus 98.5% [95% CI, 96.5–99.5]; $P=1.0$), lower specificity of rule-in (84.4% [95% CI, 79.9–88.3] versus 91.7% [95% CI, 90.5–92.9]; $P<0.001$), and lower overall efficacy (54% versus 76%, $P<0.001$; proportion ruled out, 18% versus 58%, $P<0.001$) compared with patients with normal renal function.

CONCLUSIONS: In patients with RD, the safety of the European Society of Cardiology 0/1-hour algorithm is high, but specificity of rule-in and overall efficacy are decreased. Modifications of the rule-in and rule-out thresholds did not improve the safety or overall efficacy of the 0/1-hour algorithm.

CLINICAL TRIAL REGISTRATION: URL: <https://www.clinicaltrials.gov>. Unique identifier: NCT00470587.

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Clinical Perspective

What Is New?

- The 0/1-hour algorithms using high-sensitivity cardiac troponin for rapid triage of patients with suspected myocardial infarction are increasingly used in clinical practice worldwide.
- Although their high safety and efficacy could be shown in the general, mixed setting of emergency departments, their utility in patients with renal dysfunction, presenting with elevated high-sensitivity cardiac troponin levels often in the absence of acute myocardial ischemia, has been questioned.
- For the first time, we demonstrated the excellent safety of the 0/1-hour algorithms using high-sensitivity cardiac troponin T and high-sensitivity cardiac troponin I also in patients with renal dysfunction, whereas overall efficacy and rule-in specificity were reduced compared with patients with normal renal function.

What Are the Clinical Implications?

- The investigated 0/1-hour algorithms for rapid triage of patients with suspected myocardial infarction provide high safety irrespective of renal function and do not seem to require adjustment for renal function.
- However, the proportion of patients eligible for rule-out is reduced in patients with renal dysfunction compared with patients with normal renal function (\approx factor 3) because of the substantially higher prevalence of myocardial infarction in patients with renal dysfunction (\approx factor 3).

Acute myocardial infarction (AMI) is a major cause of death and disability worldwide. Its rapid and accurate diagnosis is critical for the initiation of effective evidence-based medical management and treatment.^{1–3} In addition, its rapid and reliable rule-out has the potential to reduce the time spent in the emergency department (ED), accelerate the identification and treatment of the actual cause of chest pain, reduce patients' anxiety, and avoid substantial costs for the healthcare system.^{4,5}

For several reasons, patients with renal dysfunction merit particular attention.^{6,7} First, the incidence of AMI is increased in this vulnerable subgroup.^{8–10} Second, atypical clinical presentation of AMI may be more frequent.^{11,12} Third, left ventricular hypertrophy is common and often results in ECG changes that may mimic or obscure AMI. Fourth, patients with renal dysfunction are more prone to adverse events related to cardiovascular medication (eg, anticoagulation) as well as cardiovascular procedures, including coronary angiography and coronary intervention.^{1,2} Fifth, levels of cardiac troponin (cTn) are frequently chronically elevat-

ed even in the absence of AMI.^{6,10,13} Recently, sensitive and high-sensitivity cardiac troponin assays (hs-cTn) were demonstrated to be accurate tools in diagnosing AMI in patients with renal dysfunction, particularly when adjusted slightly higher cutoff levels are used for clinical decision making.¹⁰

The latest guidelines of the European Society of Cardiology (ESC) for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation recommend the use of a 0/1-hour algorithm to rapidly rule out and rule in non-ST-segment elevation myocardial infarction (NSTEMI) based on hs-cTn concentrations at presentation and their absolute 1-hour changes.¹ Assay-specific cutoff values are recommended for uniform application irrespective of renal function. High safety and efficacy of the 0/1-hour algorithm were demonstrated in unselected patients, of which the vast majority had normal renal function. It is unknown whether these results also apply to patients with renal dysfunction (RD).^{1,14–19} Because patients with RD frequently present with increased hs-cTn concentrations even in the absence of NSTEMI, concern has been raised regarding the performance of the 0/1-hour algorithm in RD.¹⁰

We therefore aimed to assess the diagnostic performance of the ESC 0/1-hour algorithm in patients with RD in a large prospective multicenter diagnostic study.

METHODS

Study Design and Population

APACE (Advantageous Predictors of Acute Coronary Syndrome Evaluation) is an ongoing prospective international multicenter diagnostic study with 12 centers in 5 European countries aiming to advance the early diagnosis of AMI (ClinicalTrials.gov. Unique identifier: NCT00470587).^{10,15–17,20,21} Adult patients presenting to the ED with symptoms suggestive of AMI (eg, acute chest discomfort and angina pectoris) with an onset or peak within the last 12 hours were recruited. Enrollment was independent of renal function, whereas patients with terminal kidney failure on chronic dialysis were excluded. For this analysis, patients with ST-segment elevation myocardial infarction, patients with missing creatinine measurement, patients in whom the final diagnosis remained unclear even after central adjudication and ≥ 1 elevated hs-cTnT concentration possibly indicating AMI, as well as patients with no available hs-cTnT (for dataset A) or hs-cTnI (for dataset B) concentrations determined on presentation to the ED and after 1 hour were also excluded. Dataset B represents a subset of dataset A. The most common reasons for missing samples after 1 hour were early transfer to the catheter laboratory or coronary care unit and diagnostic procedures around the 1-hour window that precluded blood draw at 1 hour.

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. Written informed consent was obtained from all patients. The authors designed the study, gathered

and analyzed the data, vouched for the data and analysis, wrote the paper, and decided to publish. The STARD Checklist (Standards for Reporting of Diagnostic Accuracy Studies) can be found in [Table 1 in the online-only Data Supplement](#).²² The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Routine Clinical Assessment

Patients underwent clinical assessment that included medical history, physical examination, and standard blood tests including serial measurements of local hs-cTn, 12-lead ECG, chest radiography, continuous ECG rhythm monitoring, and pulse oximetry. Management of patients was left to the discretion of the attending physician.

Adjudicated Final Diagnosis

Adjudication of the final diagnosis was performed by 2 independent cardiologists at the core laboratory (University Hospital Basel) applying the universal definition of AMI using 2 datasets: (1) all available medical records obtained during clinical care, including history, physical examination, results of laboratory testing including serial clinical hs-cTn levels (according to onsite used hs-cTn assay obtained from clinical blood samples), radiological testing, ECG, echocardiography, cardiac exercise test, lesion severity, and morphology in coronary angiography pertaining to the patient from the time of ED presentation to 90-day follow-up; and (2) study-specific assessments, including detailed chest pain characteristics using 34 predefined criteria, serial hs-cTnT blood concentrations obtained from study samples, and clinical follow-up by telephone or mail. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist.

AMI was defined and hs-cTn interpreted as recommended in the current guidelines.^{1–3,14} In brief, myocardial infarction was diagnosed when there was evidence of myocardial necrosis in association with a clinical setting consistent with myocardial ischemia. Myocardial necrosis was diagnosed by ≥ 1 cTn value >99 th percentile together with a significant rising or falling. The criteria used to define a rise or fall in conventional cTn and hs-cTnT are described in detail in the [Methods section in the online-only Data Supplement](#). All other patients were classified in the categories of unstable angina, noncardiac chest pain, cardiac but noncoronary disease (eg, tachyarrhythmias, perimyocarditis), and symptoms of unknown origin with normal levels of hs-cTnT.

Assessment of Renal Function

Renal function was quantified by estimating glomerular filtration rate (eGFR) with the use of the chronic kidney disease epidemiology collaboration formula based on plasma creatinine level obtained at presentation to the ED, age, sex, and ethnicity.²³ For this analysis, RD was defined as an eGFR of <60 mL/min/1.73 m.² Creatinine measurements were performed on a Roche Modular P1 analyzer with the enzymatic creatinine-peroxidase-antiperoxidase PAP method for quantification (Roche Diagnostics). Serum creatinine can be converted from micromoles per liter to milligrams per deciliter

by dividing by 88.4. Preexisting kidney dysfunction was documented based on previous hospital records and detailed patient history at the time of ED presentation.

Investigational hs-cTn Measurements

Blood samples for determination of hs-cTnT and hs-cTnI were collected into tubes containing potassium EDTA (as an anti-coagulant) or serum gel (as a clot activator) at presentation to the ED and serially thereafter. Serial sampling was discontinued when a patient was discharged or transferred to the catheter laboratory for treatment. After centrifugation, samples were either analyzed directly or frozen at -80°C until they were assayed in a blinded fashion in a dedicated core laboratory.

According to the manufacturer, the hs-cTnT assay (Elecsys 2010 high-sensitivity troponin T, Roche Diagnostics) has a 99th percentile concentration of 14 ng/L with a corresponding coefficient of variation of 10% at 13 ng/L.²⁴ Limit of blank and limit of detection have been determined to be 3 ng/L and 5 ng/L. None of the hs-cTnT measurements in this analysis were affected by the 2010 to 2012 calibration shift.^{25–28}

The hs-cTnI assay (ARCHITECT High Sensitive STAT Troponin I, Abbott Laboratories) has a 99th percentile concentration of 26.2 ng/L with a corresponding coefficient of variation of $<5\%$ and a limit of detection of 1.9 ng/L.^{29–31}

Distributions of the latest study blood samples according to time since ED presentation and time since chest pain onset are listed in [Tables II and III in the online-only Data Supplement](#).

ESC hs-cTn 0/1-Hour Algorithm

Recent studies have highlighted fundamental differences in mortality risk, pathophysiology, and benefit from early coronary angiography and intense dual-antiplatelet therapy between patients with NSTEMI and patients with true unstable angina (not including patients with small NSTEMIs missed by conventional cTn assays).^{1,32} Accordingly, the immediate task in the ED is to detect NSTEMI. Thus, the ESC 0/1-hour algorithm was designed to detect NSTEMI. The diagnosis of unstable angina is based on clinical assessment, ECG, and rule-out of NSTEMI in the ED, as well as cardiac imaging performed either in-hospital or on an outpatient basis.^{1,32}

The ESC hs-cTn 0/1-hour algorithm, which should always be used in conjunction with all clinical information available, including the ECG, triages patients presenting with suspected NSTEMI toward rule-out, observe, and rule-in based on assay-specific levels of hs-cTn obtained at presentation and after 1 hour ([Figure 1 in the online-only Data Supplement](#)).¹ The assay-specific cutoff levels were derived in diagnostic studies enrolling unselected patients with mostly normal renal function.^{1,14–19}

Main Outcome Measures

The coprimary outcome measures were safety of rule-out, accuracy of rule-in, and overall efficacy of the ESC 0/1-hour algorithm in patients with RD. Safety was quantified as sensitivity for NSTEMI in the rule-out group, accuracy as specificity for NSTEMI in the rule-in group, and overall efficacy as the proportion of patients triaged to either rule-out or rule-in

based on the 0- and 1-hour sample. Because prevalence of NSTEMI differs between patients with RD and patients with normal renal function,¹⁰ the negative predictive value (NPV) for NSTEMI in the rule-out group and the positive predictive value (PPV) in the rule-in group, which both depend on prevalence, were considered as secondary outcome measures. Additional secondary outcome measures included the proportion of patients assigned directly to rule-out or rule-in based on the single hs-cTn concentration measured at presentation.

Subgroup analyses assessing the diagnostic performance of the 0/1-hour algorithm were performed in early presenters (≤ 2 hours after chest pain onset), in patients with preexisting and new onset of RD, in women and men, and in the dataset after exclusion of patients who were part of the initial derivation cohort of the 1-hour algorithms.

To extend and corroborate the concept of the ESC 0/1-hour algorithm in patients with RD, diagnostic performance was further assessed using stepwise modified cutoff criteria optimized for patients with RD using hs-cTn concentrations at presentation or absolute changes within the first hour.

Follow-Up and Clinical End Points

Patients were contacted 3, 12, and 24 months after discharge by telephone calls or in written form. Information regarding death during follow-up was furthermore obtained from the patient's hospital notes, the family physician's records, and the national registry on mortality. The coprimary prognostic end points were overall survival after 30 days and 2 years. The secondary prognostic end point was major adverse cardiac events (MACEs), defined as the composite of all-cause mortality, AMI (including index event), cardiogenic shock, ventricular tachyarrhythmias, or higher degree atrioventricular block at 30 days.

Statistical Analysis

All data are expressed as medians (1st quartile, 3rd quartile) for continuous variables and for categorical variables as numbers and percentages. Continuous variables were compared with the Mann-Whitney U test, and categorical variables using the chi-square test or Fisher exact test as appropriate. Receiver operating characteristics curves were constructed to assess the discriminative performance throughout hs-cTn concentrations at presentation and their absolute changes in ≤ 1 hour to diagnose NSTEMI. The comparison of independent areas under the receiver operating characteristics curve was performed as recommended by Hanley and McNeil.³³

We used the cross tables derived by the application of the official ESC assay-specific cutoff criteria for rule-out or rule-in to calculate diagnostic performance parameters and their 95% confidence intervals (CI).³⁴ To compare sensitivity, specificity, NPV, PPV, and efficacy, we used a chi-square or Fisher exact test for unpaired samples and the McNemar test or the method described by Moskowitz and Pepe³⁵ for paired samples, as appropriate. Correlations between renal function and concentrations/changes of hs-cTn were determined with the use of the Spearman rank correlation based on log-transformed hs-cTn values.

Overall survival and MACE-free survival during follow-up according to the classification provided by the respective 0/1-hour algorithm were plotted in Kaplan-Meier curves, and a

log-rank test was used to assess differences in survival among groups.

Unless stated otherwise, results are reported based on dataset A. All hypothesis testing was 2-tailed, and *P* values of <0.05 were considered to indicate statistical significance without adjustments for multiple testing. All statistical analyses were performed with the use of IBM SPSS Statistics for Windows, version 23.0 (SPSS Inc), R statistical software version 3.4.1 (www.R-project.org, R Foundation for Statistical Computing), and MedCalc Statistical Software, version 17.8 (MedCalc Software bvba).

RESULTS

Patient Characteristics

From 4323 consecutively recruited patients, serial hs-cTnT measurements at presentation and after 1 hour were available in 3254 patients (dataset A, 100%) and serial hs-cTnI measurements in 2949 patients (dataset B) (Figure II in the online-only Data Supplement). Baseline characteristics are depicted in the Table 1 and Table IV in the online-only Data Supplement. Dataset B represented a subset of dataset A (overlap, 91%) (Table V in the online-only Data Supplement). Prevalence of RD was 15% (487/3254 in dataset A, 445/2949 in dataset B) with a median eGFR of 48 (37, 55) ml/min/1.73 m² as compared with 93 (81, 104) ml/min/1.73 m² in patients with normal renal function. Patients with RD differed from patients with normal renal function in multiple baseline characteristics, including higher prevalence of cardiovascular risk factors, previous myocardial infarction, and ECG abnormalities.

Adjudicated Final Diagnosis

NSTEMI was the adjudicated final diagnosis in 515 of 3254 (16%) patients. In patients with RD, prevalence of NSTEMI was 31% compared with 13% in patients with normal renal function ($P<0.001$). The prevalence of NSTEMI was significantly higher in those patients with RD who had preexisting kidney disease (37% versus 24%, $P=0.002$). Among all NSTEMIs, type 2 NSTEMI was more frequent in patients with RD compared with patients with normal renal function (22% versus 10%, $P<0.001$) (Table VI in the online-only Data Supplement), resulting in an overall type 2 NSTEMI prevalence of 6.8% (33/487) in patients with RD compared with 1.3% (35/2767) in patients with normal renal function. Also, cardiac causes other than coronary artery disease were more common in patients with RD and noncardiac causes less common compared with patients with normal renal function. Disagreement between the 2 independent cardiologists adjudicating the final diagnosis was more common in patients with RD compared with patients with normal renal function (13.1% versus 9.1%, $P=0.006$).

Table 1. Baseline Characteristics of Patients in Dataset A

	Normal Renal Function n=2767	Renal Dysfunction* n=487	P Value [†]	Renal Dysfunction (n=487)		
				NSTEMI		
				Yes (n=151)	No (n=336)	P Value [‡]
Age, y	58 (47, 70)	79 (73, 84)	<0.001	81 (75, 86)	78 (72, 83)	0.001
Sex, male	1924 (70)	284 (58)	<0.001	93 (62)	191 (57)	0.326
Risk factors						
Hypertension	1554 (56)	347 (71)	<0.001	140 (93)	299 (89)	0.202
Hypercholesterolemia	1258 (45)	347 (71)	<0.001	117 (77)	230 (68)	0.042
Diabetes mellitus	434 (16)	136 (28)	<0.001	51 (34)	85 (25)	0.054
Current smoking	770 (28)	44 (9)	<0.001	19 (13)	25 (7)	0.067
History of smoking	1001 (36)	223 (46)	<0.001	69 (46)	154 (46)	0.977
History						
Coronary artery disease	811 (29)	280 (57)	<0.001	102 (68)	178 (53)	0.003
Previous myocardial infarction	576 (21)	204 (42)	<0.001	82 (54)	122 (36)	<0.001
Previous revascularization	695 (25)	209 (43)	<0.001	73 (48)	136 (40)	0.105
Peripheral artery disease	110 (4)	62 (13)	<0.001	26 (17)	36 (11)	0.046
Previous stroke	123 (4)	58 (12)	<0.001	23 (15)	35 (10)	0.129
Vital status						
Heart rate, bpm	76 (66, 89)	75 (64, 91)	0.519	81 (70, 97)	73 (63, 88)	0.001
Systolic blood pressure, mm Hg	142 (127, 158)	138 (121, 156)	0.001	135 (123, 157)	139 (121, 156)	0.556
Diastolic blood pressure, mm Hg	82 (73, 92)	73 (64, 84)	<0.001	73 (63, 83)	74 (64, 85)	0.549
Body mass index, kg/m ²	26 (24, 30)	27 (24, 30)	0.285	26 (23, 28)	27 (25, 31)	<0.001
Electrocardiographic findings						
Left bundle-branch block	76 (3)	48 (10)	<0.001	21 (14)	27 (8)	0.044
ST-segment depression	192 (7)	74 (15)	<0.001	38 (25)	36 (11)	<0.001
T-wave inversion	288 (10)	84 (17)	<0.001	37 (25)	47 (14)	0.004
Laboratory measurements						
Serum creatinine, μmol/l	73 (63, 83)	118 (101, 140)	<0.001	123 (106, 151)	116 (99, 135)	0.002
Estimated GFR ml/min/1.73 m ²	93 (81, 104)	48 (37, 55)	<0.001	45 (34, 52)	49 (39, 55)	<0.001
Hours since CPO	5 (2, 14)	6 (3, 12)	0.018	6 (3, 12)	6 (3, 14)	0.417
Distribution of time since CPO						
≤2 h after CPO	731 (27)	97 (20)	0.002	35 (23)	62 (19)	0.550
≤3 h after CPO	1031 (37)	144 (30)	<0.001	47 (32)	97 (29)	
>3 h to ≤6 h after CPO	561 (20)	117 (24)	0.060	37 (25)	80 (24)	
>6 h after CPO	1158 (42)	226 (46)	0.146	67 (44)	159 (47)	

CPO indicates chest pain onset; GFR, glomerular filtration rate; and NSTEMI, non-ST-segment elevation myocardial infarction. Categorical variables are presented as numbers (%); continuous variables are presented as medians (quartile 1, quartile 3). Continuous variables were compared with the Mann-Whitney U test and categorical variables using the Pearson chi-square test or Fisher exact test as appropriate.

*Renal dysfunction was diagnosed if the estimated GFR was <60 mL/min/1.73 m² using the chronic kidney disease epidemiology collaboration formula based on plasma creatinine levels obtained at presentation to the emergency department, age, sex, and ethnicity.

[†]For comparisons between patients with normal renal function and renal dysfunction.

[‡]For comparisons between patients with and without acute myocardial infarction in the subset of patients with renal dysfunction.

Hs-cTn Concentrations at Presentation and 1-Hour Changes According to Renal Function and Final Diagnosis

In patients with RD and patients with normal renal function, hs-cTn concentrations at presentation as well as absolute 1-hour changes were significantly higher in

NSTEMI compared with other final diagnoses ($P<0.001$ for all comparisons, data not shown).

In patients with final diagnoses other than NSTEMI, hs-cTnT and hs-cTnI concentrations at presentation as well as absolute 1-hour changes showed a strong, inverse correlation with eGFR, which was not observed in NSTEMI (Figure III in the online-only Data Supplement).

Table 2. Performance of the European Society of Cardiology 0/1-Hour Algorithm in Patients With Renal Dysfunction and Normal Renal Function

Using High-Sensitivity Cardiac Troponin T	Renal Dysfunction (n=487)	Normal Renal Function (n=2767)	P Value*
Prevalence of NSTEMI	31	13	<0.001
Sensitivity of rule-out	100.0 (97.6–100.0)	99.2 (97.6–99.8)	0.559
NPV of rule-out	100.0 (n.a.)	99.8 (99.5–100.0)	1.0
Specificity of rule-in	88.7 (84.8–91.9)	96.5 (95.7–97.2)	<0.001
PPV of rule-in	76.5 (70.6–81.6)	77.1 (73.1–80.7)	0.886
Proportion ruled out	18.1 (14.6–21.6)	67.9 (66.4–69.6)	<0.001
Based on 0-hour sample only	1.4 (0.4–2.6)	17.9 (16.6–19.3)	<0.001
Based on 0/1-hour samples	16.6 (13.5–20.0)	50.0 (48.2–51.9)	<0.001
Proportion ruled in	33.3 (29.3–37.5)	13.3 (12.0–14.6)	<0.001
Based on 0-hour sample only	25.9 (22.4–29.7)	8.0 (7.0–9.0)	<0.001
Based on 1-hour change	7.4 (5.2–9.6)	5.3 (4.5–6.1)	0.066
Overall efficacy	51.3 (46.8–55.8)	81.2 (79.8–82.6)	<0.001
Prevalence of NSTEMI in the observational group	11 (7–15)	15 (12–18)	0.186

Numbers represent percentage (95% confidence interval).

n.a. indicates not applicable; NPV, negative predictive value; NSTEMI, non-ST-segment elevation myocardial infarction; and PPV, positive predictive value. *Performances measures in patients with renal dysfunction and normal renal function were compared using the chi-square or Fisher exact test.

The diagnostic accuracy of hs-cTnT and hs-cTnI concentrations at presentation for NSTEMI, as quantified by the areas under the receiver operating characteristics curve, was high among patients with RD (for hs-cTnT, 0.87 [95% CI, 0.84–0.90]; for hs-cTnI, 0.86 [95% CI, 0.83–0.90]) but even significantly higher in patients with normal renal function (for hs-cTnT, 0.94 [95% CI, 0.93–0.95]; for hs-cTnI, 0.93 [95% CI, 0.92–0.95]) (Figure IV in the online-only Data Supplement). Smaller dif-

ferences were observed for the diagnostic accuracy of the absolute 1-hour change in hs-cTn.

Performance of the ESC 0/1-Hour Algorithm Using hs-cTnT in RD

Safety of rule-out by the ESC 0/1-hour algorithm, quantified as the sensitivity for NSTEMI in the rule-out group, was high in patients with RD and similar to

Table 3. Performance of the European Society of Cardiology 0/1-Hour Algorithm in Patients With Renal Dysfunction and Normal Renal Function

Using High-Sensitivity Cardiac Troponin I	Renal Dysfunction (n=445)	Normal Renal Function (n=2504)	P Value
Prevalence of NSTEMI	32	13	<0.001
Sensitivity of rule-out	98.6 (95.0–99.8)	98.5 (96.5–99.5)	1.0
NPV of rule-out	97.4 (90.5–99.4)	99.7 (99.2–99.9)	0.046
Specificity of rule-in	84.4 (79.9–88.3)	91.7 (90.5–92.9)	<0.001
PPV of rule-in	70.8 (64.8–76.2)	60.7 (57.1–64.2)	0.023
Proportion ruled out	17.5 (13.9–21.4)	57.8 (55.8–59.8)	<0.001
Based on 0-hour sample only	1.3 (0.4–2.5)	10.9 (9.7–12.1)	<0.001
Based on 0/1-hour samples	16.2 (12.7–19.7)	46.9 (44.7–48.9)	<0.001
Proportion ruled in	36.2 (31.6–40.8)	18.3 (16.8–19.8)	<0.001
Based on 0-hour sample only	27.0 (23.1–30.9)	12.9 (11.5–14.2)	<0.001
Based on 1-hour change	9.2 (6.5–12.0)	5.4 (4.6–6.4)	0.002
Overall efficacy	53.5 (49.2–58.0)	76.1 (74.5–77.8)	<0.001
Prevalence of NSTEMI in the observational group	13 (9–18)	8 (6–10)	0.021

Numbers represent percentage (95% confidence interval).

n.a. indicates not applicable; NPV, negative predictive value; NSTEMI, non-ST-segment elevation myocardial infarction; and PPV, positive predictive value. *Performances measures in patients with renal dysfunction and normal renal function were compared using the chi-square or Fisher exact test.

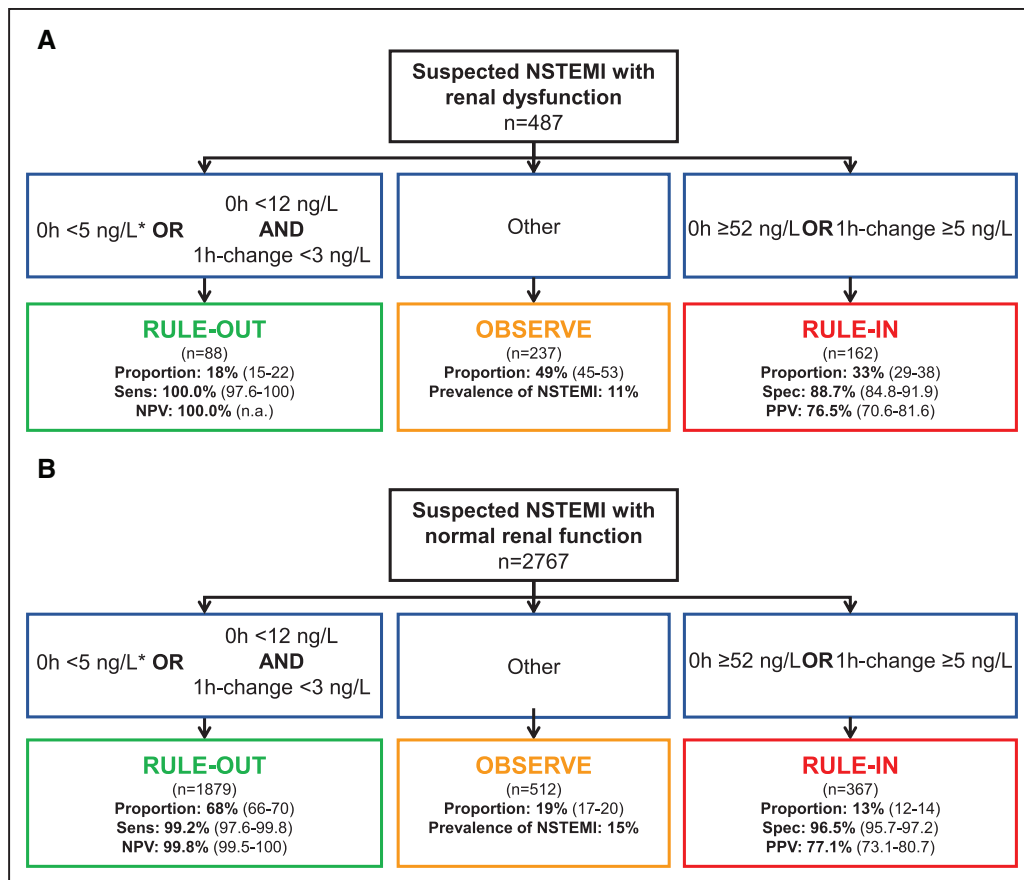


Figure 1. Performance of the European Society of Cardiology 0/1-hour algorithm using high-sensitivity cardiac troponin T in patients with renal dysfunction and normal renal function.

Flow charts depicting the diagnostic performance of the European Society of Cardiology 0/1-hour algorithm for rule-out and rule-in of non-ST-segment elevation myocardial infarction in (A) patients with renal dysfunction (defined as an estimated glomerular filtration rate <60 mL/min/1.73 m²), and (B) patients with normal renal function using high-sensitivity cardiac troponin T (hs-cTnT, Elecsys analyzer). 1h-change indicates absolute (unsigned) change of high-sensitivity cardiac troponin within 1 hour; n.a., not applicable; NPV, negative predictive value; NSTEMI, non-ST-segment elevation myocardial infarction; PPV, positive predictive value; Sens, Sensitivity; and Spec, specificity. *If chest pain onset >3 hours before presentation to the emergency department.

patients with normal renal function using hs-cTnT (100% [95% CI, 97.6–100] versus 99.2% [95% CI, 97.6–99.8], respectively; $P=0.559$) (Table 2 and Figure 1). NPV was 100% in patients with RD compared with 99.8% (95% CI, 99.5–100) in patients with normal renal function ($P=1.0$).

Accuracy of rule-in, quantified as the specificity for NSTEMI in the rule-in group, was lower in patients with RD compared with patients with normal renal function (88.7% [95% CI, 84.8–91.9] versus 96.5% [95% CI, 95.7–97.2], $P<0.001$). Because of the higher prevalence of NSTEMI in patients with RD, accuracy of rule-in as quantified by PPV remained comparable in patients with RD and patients with normal renal function (PPV, 76.5% [95% CI, 70.6–81.6] versus 77.1% [95% CI, 73.1–80.7], $P=0.886$). Unstable angina ($n=2$ and 1), myocarditis ($n=0$ and 14), Tako-Tsubo cardiomyopathy ($n=1$ and 4), and acute heart failure ($n=11$

and 6) accounted for 37% and 30% of non-NSTEMI diagnoses in the rule-in groups of patients with RD and normal renal function, respectively ($P=0.445$ for comparison).

Efficacy of rule-out, quantified as the proportion of patients assigned toward rule-out based on the 0- and 1-hour samples, was substantially lower in patients with RD compared with patients with normal renal function (18.1% [95% CI, 14.6–21.6] versus 67.9% [95% CI, 66.4–69.6], $P<0.001$). Direct rule-out, based on a single hs-cTn concentration measured at presentation in patients presenting >3 hours after chest pain onset, was feasible in 1.4% (95% CI, 0.4–2.6) of patients with RD compared with 17.9% (95% CI, 16.6–19.3) of patients with normal renal function ($P<0.001$). Efficacy of rule-in was substantially higher in patients with RD compared with patients with normal renal function (33.3% [95% CI, 29.3–37.5] versus



Figure 2. Performance of the European Society of Cardiology 0/1-hour algorithm using high-sensitivity cardiac troponin T in different stages of renal function.

hs-cTnT indicates high-sensitivity cardiac troponin T; and NSTEMI, non-ST-segment elevation myocardial infarction.

13.3% [95% CI, 12.0–14.6], $P < 0.001$). Overall efficacy, quantified as the proportion of patients assigned to either rule-out or rule-in in ≤ 1 hour, was substantially lower in patients with RD compared with patients with normal renal function (51.3% [95% CI, 46.8–55.8] versus 81.2% [95% CI, 79.8–82.6], $P < 0.001$). Prevalence of NSTEMI in the observe group was comparable in patients with RD compared with patients with normal renal function (11% versus 15%, $P = 0.186$). No NSTEMI patient with RD was incorrectly ruled out by the ESC 0/1-hour algorithm, whereas 3 NSTEMI patients (0.1%) with normal renal function were missed (Table VII in the online-only Data Supplement). The diagnostic performance of the ESC hs-cTnT 0/1-hour algorithm according to different stages of renal dysfunction is depicted in Figure 2.

Performance of the ESC 0/1-Hour Algorithm Using hs-cTnI in RD

Safety of rule-out by the ESC 0/1-hour algorithm was high in patients with RD and similar to patients with normal renal function using hs-cTnI (98.6% [95% CI, 95.0–99.8] versus 98.5% [95% CI, 96.5–99.5], respectively; $P = 1.0$) (Table 3 and Figure 3). NPV (and the prevalence of non-NSTEMI) was lower in patients with RD (NPV, 97.4% [95% CI, 90.5–99.4]) compared with patients with normal renal function (NPV, 99.7% [95% CI, 99.2–99.9], $P = 0.046$).

Accuracy of rule-in as quantified by specificity was lower in patients with RD compared with patients with normal renal function (specificity, 84.4% [95% CI, 79.9–88.3] versus 91.7% [95% CI, 90.5–92.9], $P < 0.001$).

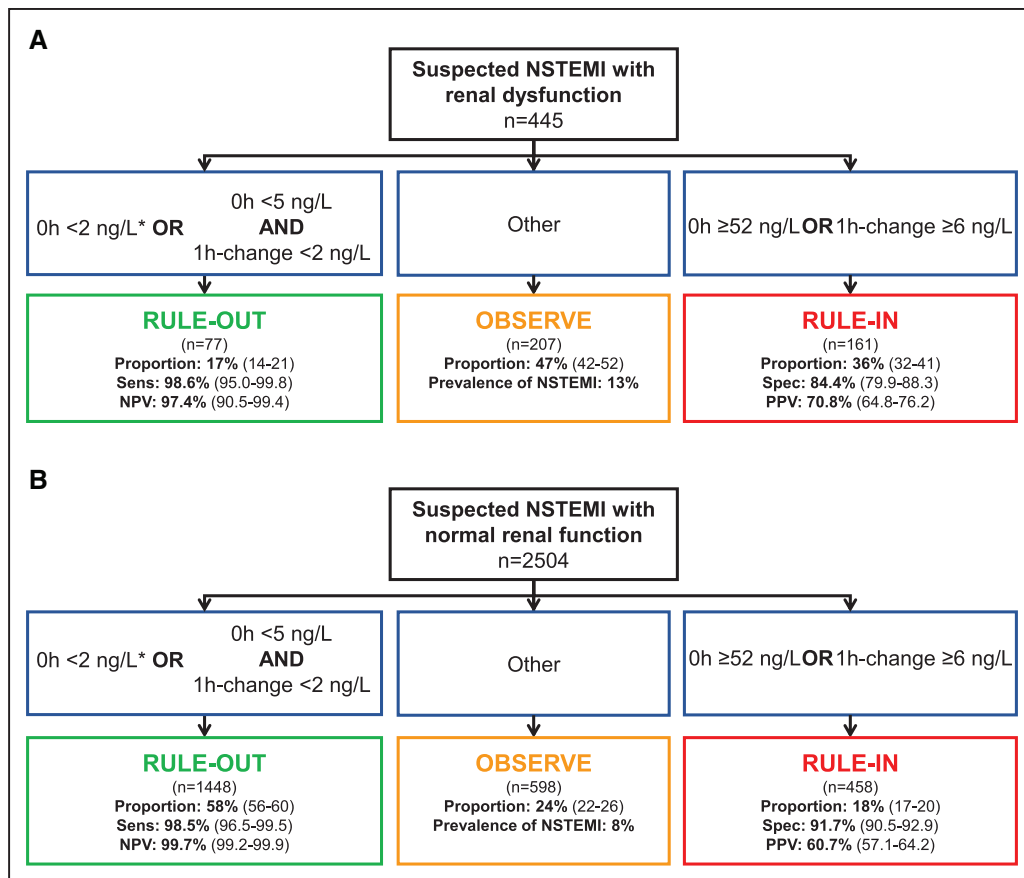


Figure 3. Performance of the European Society of Cardiology 0/1-hour algorithm using high-sensitivity cardiac troponin I in patients with renal dysfunction and normal renal function.

Flow charts depicting the diagnostic performance of the European Society of Cardiology 0/1-hour algorithm for rule-out and rule-in of non-ST-segment elevation myocardial infarction in patients with (A) renal dysfunction and (B) normal renal function using high-sensitivity cardiac troponin I (hs-cTnI, Architect analyzer). 1-h change indicates absolute (unsigned) change of high-sensitivity cardiac troponin within 1 hour; NPV, negative predictive value; NSTEMI, non-ST-segment elevation myocardial infarction; PPV, positive predictive value; Sens, sensitivity; and Spec, specificity. *If chest pain onset >3 hours before presentation to the emergency department.

However, because of the higher prevalence of NSTEMI in patients with RD, accuracy as quantified by PPV of rule-in was higher in patients with RD compared with patients with normal renal function (PPV, 70.8% [95% CI, 64.8–76.2] versus 60.7% [95% CI, 57.1–64.2], $P=0.023$). Unstable angina ($n=8$ and 30), myocarditis ($n=0$ and 15), Tako-Tsubo cardiomyopathy ($n=1$ and 4), and acute heart failure ($n=10$ and 15) accounted for 40% and 36% of non-NSTEMI diagnoses in the rule-in groups of patients with RD and patients with normal renal function, respectively ($P=0.614$ for comparison).

Efficacy of rule-out was substantially lower in patients with RD compared with patients with normal renal function (17.5% [95% CI, 13.9–21.4] versus 57.8% [95% CI, 55.8–59.8], $P<0.001$). Direct rule-out was feasible in 1.3% (95% CI, 0.4–2.5) of patients with RD compared with 10.9% (95% CI, 9.7–12.1) of patients with normal renal function ($P<0.001$). Efficacy of rule-in was higher in patients with RD compared with patients with normal renal function (36.2% [95%

CI, 31.6–40.8] versus 18.3% [95% CI, 16.8–19.8], $P<0.001$). Overall efficacy was substantially lower in patients with RD compared with patients with normal renal function (53.5% [95% CI, 49.2–58.0] versus 76.1% [95% CI, 74.5–77.8], $P<0.001$). Prevalence of NSTEMI in the observational group was lower in patients with RD compared with patients with normal renal function (13% versus 18%, $P=0.021$). Two patients with NSTEMI (0.4%) with RD were incorrectly ruled out by the ESC 0/1-hour algorithm, whereas 5 patients with NSTEMI (0.2%) with normal renal function were missed (Table VIII in the online-only Data Supplement). Diagnostic performance of the ESC hs-cTnI 0/1-hour algorithm according to different stages of RD is depicted in Figure 4.

Performance of the ESC 0/1-Hour Algorithm in Different Subgroups

Robust and highly comparable findings were observed in subgroup and sensitivity analyses performed in pa-

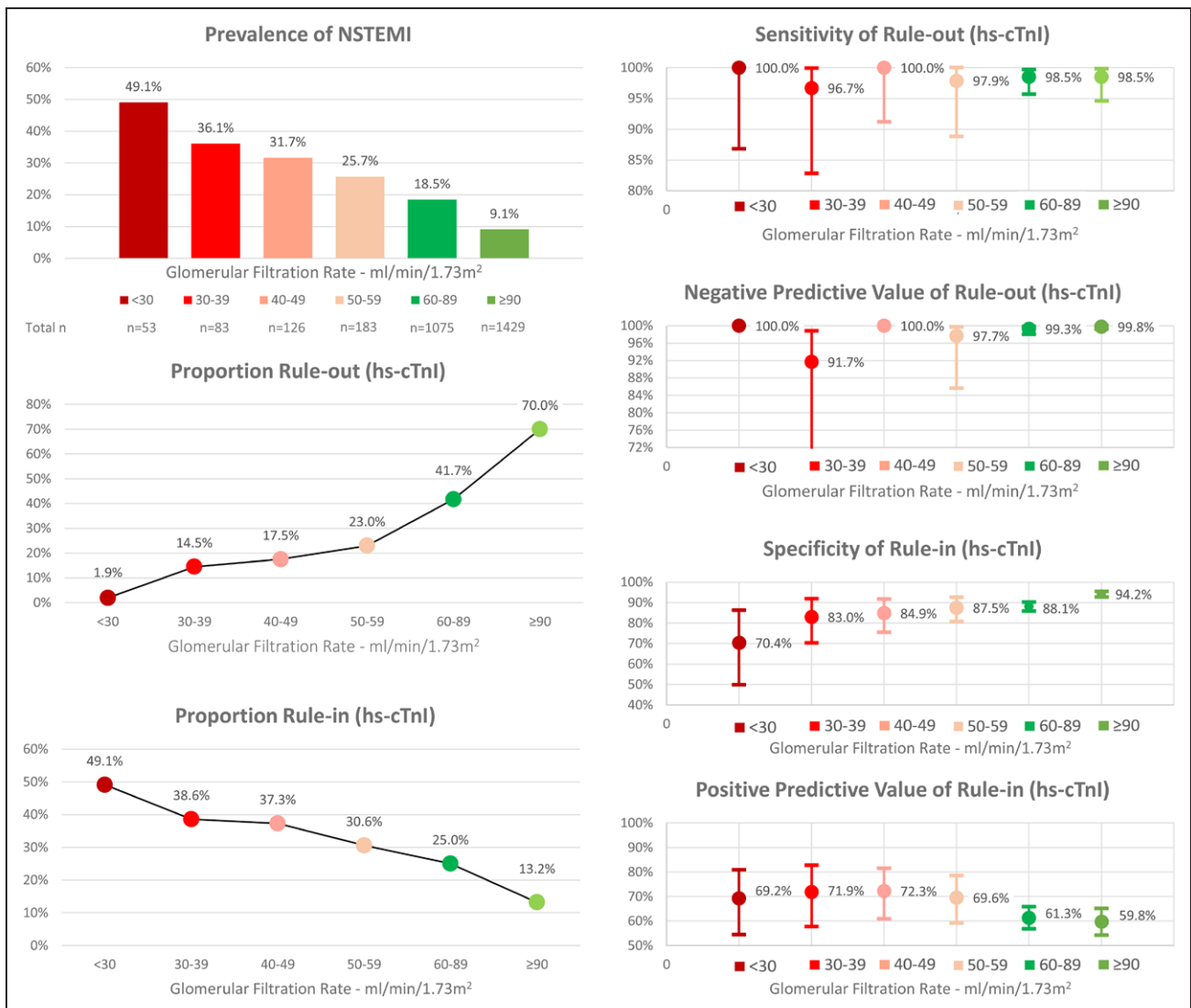


Figure 4. Performance of the European Society of Cardiology 0/1-hour algorithm using high-sensitivity cardiac troponin I in different stages of renal function.

hs-cTnI indicates high-sensitivity cardiac troponin I; and NSTEMI, non-ST-segment elevation myocardial infarction.

tients presenting within the first 2 hours after chest pain onset, in patients with preexisting and new-onset of renal dysfunction, and in women and men as well as in the study dataset after exclusion of patients who were part of the original derivation cohorts of the 2 investigated 0/1-hour algorithms. Details on the diagnostic performance of the ESC 0/1-hour algorithms in the various subgroups are listed in Tables IX–XII in the online-only Data Supplement.

Modifications of the 0/1-Hour Algorithm to Optimize Rule-Out Efficacy and Rule-In Specificity in Patients With RD

Stepwise increase of the official ESC assay-specific cutoff criteria for rule-out of NSTEMI resulted in increasing rule-out efficacy, however at the cost of rule-

out safety. Stepwise increase of the official ESC assay-specific cutoff criteria for rule-in of NSTEMI resulted in increasing specificity of rule-in, however at the cost of rule-in efficacy (Tables XIII and XIV in the online-only Data Supplement). Among the numerous possible cutoff criteria combinations, 1 specific cutoff value combination for rule-out, preserving the same sensitivity as the official ESC cutoff value combination, as well as 1 specific cutoff value combination for rule-in, was chosen for each hs-cTn assay to compare its performance with the official ESC 0/1-hour algorithm (Table XV and Figures V and VI in the online-only Data Supplement). Cutoff concentrations optimized for RD increased rule-out efficacy and rule-in specificity by 4.5% ($P<0.001$) and 3.9% ($P<0.001$), respectively, for hs-cTnT and by 4.7% ($P<0.001$) and 3.7%, ($P=0.001$) respectively, for hs-cTnI. However, because improved

rule-in specificity was obtained at the cost of rule-in efficacy, overall efficacy could not be optimized with the modified 0/1-hour algorithm (for hs-cTnT, -1.0% , $P=0.568$; for hs-cTnI, $+1.1\%$, $P=0.500$).

Prognostic Performance of the ESC 0/1-Hour Algorithm

Median follow-up time was 749 days (418, 847). Estimated overall-survival was 99.2% at 30 days and 94.3% at 2 years. Particularly in patients with RD, the ESC 0/1-hour algorithm using hs-cTnT and hs-cTnI allowed a powerful discrimination between high versus moderate and low probability of short-term (30 days) and midterm (2 years) overall survival and short-term (30 days) MACE-free survival in the respective rule-out, observe, and rule-in groups (all log-rank P values <0.001) (Figure 5 and Figure VII in the online-only Data Supplement).

DISCUSSION

This prospective, multicenter diagnostic study enrolling unselected patients presenting with acute chest discomfort to the ED used central adjudication to assess the performance of the ESC 0/1-hour algorithm in patients with RD. We report 8 major findings.

First, patients with RD presenting with acute chest discomfort to the ED had NSTEMI >2 times as often and type 2 NSTEMI even >5 times as often as patients with normal renal function. This observation extends and corroborates previous studies indicating that RD is not only commonly associated with coronary artery disease but also hypertensive heart disease and other structural cardiac disorders prone to developing the triggers of type 2 myocardial infarction, such as tachyarrhythmias, hypertension, and anemia.^{8–10,36,37}

Second, hs-cTn concentrations at presentation and their absolute 1-hour changes correlated strongly and inversely with eGFR in patients with diagnoses other than NSTEMI but not NSTEMI. Third, in patients with RD, the diagnostic performance of hs-cTn concentrations at presentation was high (areas under the receiver operating characteristics curve, 0.86–0.87) and further increased on using absolute 1-hour hs-cTn changes (areas under the receiver operating characteristics curve, 0.88–0.92).

Fourth, and likely of utmost importance, the safety of the official ESC 0/1-hour algorithm was high in patients with RD (sensitivity, 98.6–100) and comparable to patients with normal renal function (sensitivity, 98.5–99.2) irrespective of whether hs-cTnT or hs-cTnI was used. However, the efficacy of rule-out was substantially reduced in patients with RD and allowed the early rule-out in 18% of patients only.

Fifth, because of the higher proportions of patients with elevated levels of hs-cTn even in the absence of NSTEMI, specificity of rule-in was lower in patients with RD (84.4–88.7) compared with patients with normal renal function (91.7–96.5). However, the higher prevalence of NSTEMI in patients with RD also increased rule-in efficacy while maintaining high PPV of rule-in. The performance measures (mainly the PPV) of the ESC hs-cTnT 0/1-hour algorithm and the ESC hs-cTnI 0/1-hour algorithm showed subtle but consistent differences to the advantage of hs-cTnT. These differences are at least in part caused by the fact that serial measurements of hs-cTnT but not hs-cTnI were part of the extensive clinical information available for the adjudication of the final diagnosis in all patients. Accordingly, our methodology provided the most accurate and valid estimates for the ESC hs-cTnT 0/1-hour algorithm but possibly slightly underestimated the true performance of the ESC hs-cTnI 0/1-hour algorithm.

Sixth, overall efficacy allowing triage toward rule-out or rule-in based on the 0/1-hour samples was substantially reduced in patients with RD (51.3–53.5) compared with patients with normal renal function (76.1–81.2). This difference was driven by the substantial reduction in rule-out efficacy that could only partly be compensated for by the increase of rule-in efficacy. As a consequence, the percentage of patients remaining in the observe zone and usually requiring additional diagnostic tests including a 3-hour sample of hs-cTn and cardiac imaging is nearly twice as high in patients with RD compared with patients with normal renal function.

Seventh, using slightly higher cutoff concentrations of hs-cTn as an attempt to increase rule-out efficacy and rule-in specificity only partly helped to overcome the challenges posed by RD. The high pretest probability for NSTEMI in patients with RD challenges the derivation of an alternative 0/1-hour algorithm that would balance rule-out efficacy and rule-in specificity substantially better than the official ESC 0/1-hour algorithm without losing safety. It is a matter of debate how much increase of rule-out efficacy at the cost of rule-out safety or how much increase of rule-in specificity at the cost of rule-in efficacy would be acceptable. The use of alternative cutoff criteria combinations yielded rather small improvements even though they were tested in a derivation setting unblinded to the outcome NSTEMI. Accordingly, the observed small improvements in efficacy when using alternative cutoffs are associated with a potential systematic bias toward overestimating the real improvements, which might be even smaller in subsequent external validation in an independent study. Therefore, and because safety and simplicity are the most important characteristics of any diagnostic algorithm, the findings of this study recommend the use of the official ESC 0/1-hour algorithm in patients with RD until information technology-based decision tools integrating all available information (eg, age, sex, serial hs-cTn measurements, renal function) become

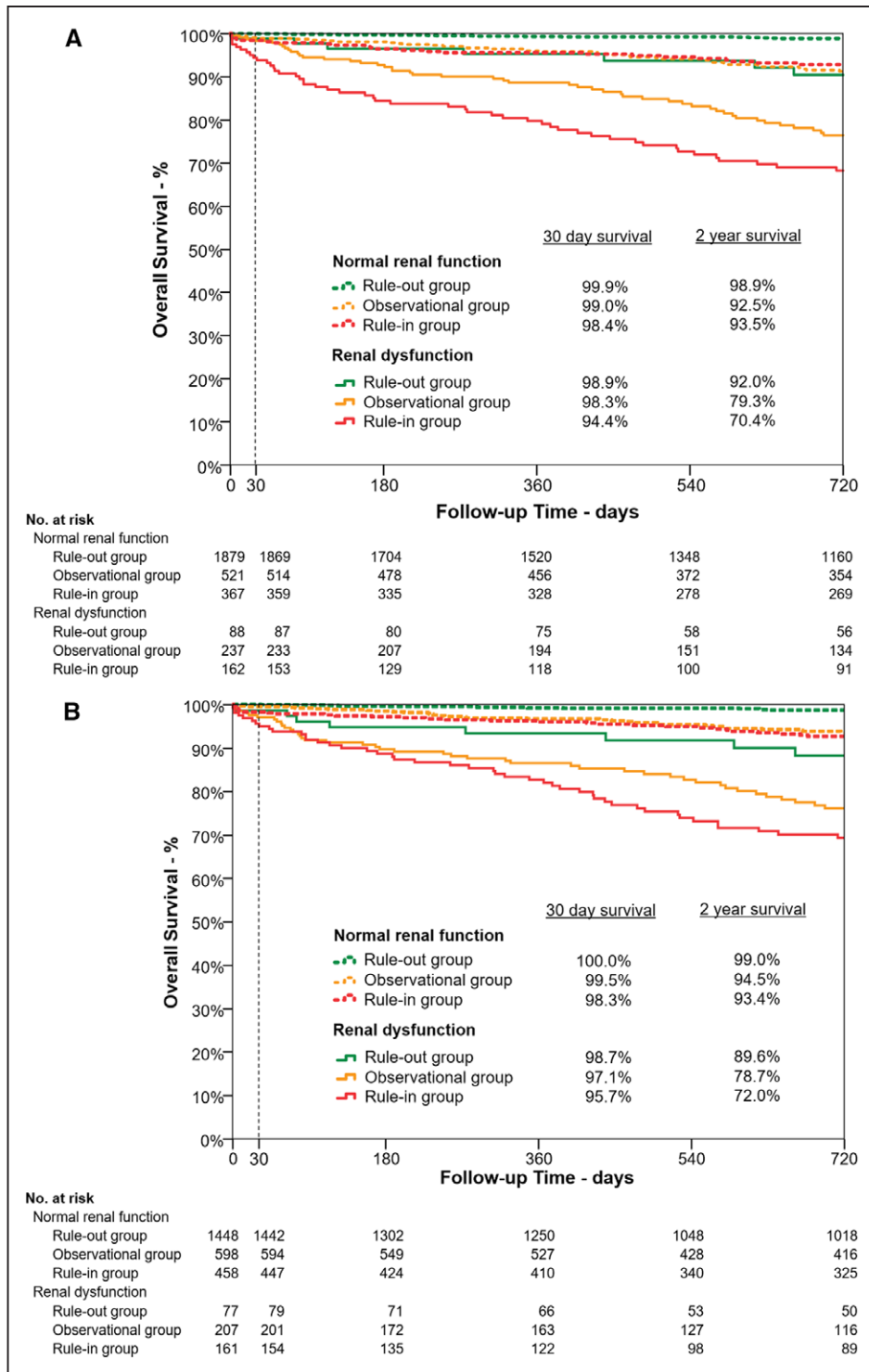


Figure 5. Short- and midterm survival according to risk stratification group by the European Society of Cardiology 0/1-hour algorithm using high-sensitivity cardiac troponin T and I in patients with normal renal function and renal dysfunction.

Kaplan-Meier curves depicting overall survival within 30 and 720 days for patients with normal renal function (dashed lines) and renal dysfunction (solid lines) stratified by the European Society of Cardiology 0/1-hour algorithm to the rule-out (green lines), observational (orange lines), and rule-in (red lines) groups. **A**, Using high-sensitivity cardiac troponin T. **B**, Using high-sensitivity cardiac troponin I.

available in clinical routine. The PPV for NSTEMI in patients assigned toward rule-in and thereby early coronary angiography would still be considered high enough by most experts, particularly given the difficulty of obtaining similar diagnostic certainty in patients with moderate elevations in cTn without coronary angiography.

Eighth, the ESC 0/1-hour algorithm allowed a powerful discrimination between high versus moderate and lower probability of short- and midterm overall survival as well as short-term MACE-free survival in the respective rule-out, observe, and rule-in groups also in patients with RD. The rather high rate of all-cause mortality during follow-up and MACE within 30 days of patients in the observe zone can be explained by the high incidence of chronic diseases in those patients, such as chronic heart failure, which are associated with high rates of both overall mortality and MACE within 30 days. These findings extend and corroborate previous studies addressing the multitude of major unmet clinical needs in the often elderly patients with RD.^{8–10,38}

Many of these challenges are related to the high prevalence of common yet undiagnosed cardiac comorbidities including hypertensive heart disease and diabetic cardiomyopathy associated with chronic cardiomyocyte injury and therefore increases in hs-cTn plasma concentrations and an increased prevalence of ECG abnormalities in patients with RD. The exact underlying pathophysiological mechanisms are incompletely understood. The contribution of cardiomyocyte injury to elevated plasma concentrations of hs-cTn in RD seems to be far greater than that of impaired renal clearance, particularly because the molecular size of the intact molecule is too large to be filtrated by glomeruli.^{36,37,39–41} Although cTn molecules may be degraded into smaller fragments that are small enough to be filtered by the kidney,⁴² the renal elimination and half-life of these cTn fragments seem to be similar in patients with RD and patients with normal renal function.⁴³ In addition, in patients with end-stage renal disease and only minimal remaining endogenous renal function, successful renal transplantation leads to a substantial reduction and often normalization of serum creatinine but no relevant change in plasma concentrations of cTnI.³⁹ It has been hypothesized that the underlying mechanism of chronic cTn release is associated with a cardiorenal syndrome triggered by some inflammatory processes leading to chronic cardiomyocyte injury and cTn release in RD.^{44,45}

Initial pilot studies evaluating the use of single cutoff concentrations suggested that in patients with RD, adjusted higher hs-cTn concentrations might provide a better balance between sensitivity and specificity compared with the 99th percentiles or the optimal single-cutoff concentration derived in patients with normal renal function.¹⁰ Meanwhile, the clinical use of hs-cTn has advanced, and current guidelines recommend the integrated use of baseline hs-cTn concentrations and

their absolute changes during serial sampling, as incorporated in the ESC 0/1-hour algorithm.¹ In contrast to a single cutoff strategy, the ESC 0/1-hour algorithm triages patients toward 1 of 3 strata: rule-out, observe, or rule-in. Assessing the possible use of adjusted higher hs-cTn concentrations within this state-of-the-art concept in patients with RD revealed pros and cons.

To the best of our knowledge, this is the first study investigating in detail the diagnostic performance of the ESC 0/1-hour algorithm in the vulnerable patient population with RD, extending the excellent performance characteristics observed in patients with overwhelmingly normal renal function.^{16–21} We cannot generalize our findings to patients with terminal kidney failure on chronic dialysis because they were excluded from this study. Additionally, our study was conducted in patients at the ED with symptoms suggestive of AMI. Further studies are required to quantify the utility of the ESC 0/1-hour algorithm in patients with either higher (eg, in a coronary care unit setting) or lower (eg, in a general practitioner setting) pretest probability for AMI.

Some limitations merit consideration when interpreting these findings. First, although we used the most stringent methodology to adjudicate the presence or absence of NSTEMI, including central adjudication by experienced cardiologists, imaging, and serial measurements of hs-cTn, we still may have misclassified a small number of patients.^{3,14} Second, to reflect the clinical information available to the ED physician when interpreting hs-cTn concentrations, we classified RD according to eGFR based on the serum creatinine concentrations obtained at ED presentation. Accordingly, this classification differs from the definition of chronic kidney disease, which would require RD to be present for 3 months.⁴⁶ Third, the chronic kidney disease epidemiology collaboration formula was used to estimate GFR irrespective of age. However, the chronic kidney disease epidemiology collaboration formula was primarily validated in patients <70 years of age.

In conclusion, in patients with RD, the safety of the ESC 0/1-hour algorithm is high, but the specificity of rule-in and overall efficacy are decreased. Modifications of cutoffs can only partly overcome the challenges of RD.

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DISCLOSURES

The authors designed the study, gathered and analyzed the data, vouch for the data and analysis, wrote the paper, and decided to publish. Drs Twerenbold and Mueller had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. All authors have read and approved the manuscript. The sponsors had no role in designing or conducting the study and no role in gathering or analyzing the data or writing the manuscript. The manuscript and its contents have not been published previously and are not being considered for publications elsewhere in whole or in part in any language, including publicly accessible web sites or e-print servers. Dr Twerenbold received research support from the Swiss National Science Foundation (P300PB_167803), the University Hospital Basel, the University of Basel, and the Cardiovascular Research Foundation Basel, as well as speaker honoraria/consulting honoraria from Abbott, Brahms, Siemens, Singulex, and Roche. Dr Boeddinghaus received speaker honoraria from Siemens. Dr Rubini received speaker honoraria from Abbott and research grants from the Swiss Heart Foundation. Dr Reichlin received research grants from the Goldschmidt-Jacobson-Foundation, the Swiss National Science Foundation (PASMP3-136995), the Swiss Heart Foundation, the Professor Max Cloëtta Foundation, the Uniscientia Foundation Vaduz, the University of Basel, and the Department of Internal Medicine, University Hospital Basel, as well as speaker honoraria from Brahms and Roche. Dr Mueller received research support from the Swiss National Science Foundation, the Swiss Heart Foundation, the Kommission für Technologie und Innovation, the Stiftung für kardiovaskuläre Forschung Basel, Abbott, Alere, AstraZeneca, Beckman Coulter, Biomerieux, Brahms, Roche, Siemens, Singulex, Spingotec, and the Department of Internal Medicine, University Hospital Basel, as well as speaker honoraria/consulting honoraria from Abbott, Alere, AstraZeneca, Biomerieux, Boehringer Ingelheim, Bristol-Myers Squibb, Brahms, Cardioentis, Novartis, Roche, Siemens, and Singulex. The other authors report no conflicts.

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FOOTNOTES

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