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Citation for published version (APA):

Document license:
TAVERNE

DOI:
10.1016/j.cca.2020.01.025

Document status and date:
Published: 01/05/2020

Document Version:
Publisher’s PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:
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Detecting patients with PMI post-CABG based on cardiac troponin-T profiles: A latent class mixed modeling approach

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ARTICLE INFO

Keywords:
Coronary artery bypass grafting
Perioperative myocardial infarction
Cardiac troponin
Profiles
Kinetics
Unsupervised statistical learning
Latent class linear mixed models
Growth mixture models

ABSTRACT

Background: Diagnosis of perioperative myocardial infarction (PMI) after coronary artery bypass grafting (CABG) is fraught with complexity since it is primarily based on a single cut-off value for cardiac troponin (cTn) that is exceeded in over 90% of CABG patients, including non-PMI patients. In this study we applied an unsupervised statistical modeling approach to uncover clinically relevant cTn release profiles post-CABG, including PMI, and used this to improve diagnostic accuracy of PMI.

Methods: In 624 patients that underwent CABG, cTnT concentration was serially measured up to 24 h post aortic cross clamping. 2857 cTnT measurements were available to fit latent class linear mixed models (LCMMs).

Results: Four classes were found, described by: normal, high, low and rising cTnT release profiles. With the clinical diagnosis of PMI as golden standard, the rising profile had a diagnostic accuracy of 97%, compared to 83% for an optimally chosen cut-off and 21% for the guideline recommended cut-off value.

Conclusion: Clinically relevant subgroups, including patients with PMI, can be uncovered using serially measured cTnT and a LCMM. The LCMM showed superior diagnostic accuracy of PMI. A rising cTnT profile is potentially a better criterion than a single cut-off value in diagnosing PMI post-CABG.

1. Introduction

Coronary artery bypass grafting (CABG) surgery is an effective procedure to treat ischemic heart disease. Although the safety of CABG surgery is well-established, the procedure is nevertheless associated with a risk of perioperative and postoperative mortality and morbidity. Elevation of cardiac biomarkers such as creatine kinase and cardiac troponin (cTn) is common following CABG surgery and reflects perioperative myocardial damage [1,2]. Even small enzyme elevations post-CABG are predictive of long-term prognosis and there is a graded association of elevation with outcome [1]. Perioperative myocardial damage can be ascribed to multiple causes, including direct trauma from surgical handling, inadequate myocardial protection during cardiopulmonary bypass or perioperative myocardial infarction (PMI) [3].

In CABG surgery, PMI is a complication that adversely affects the prognosis of the patient [3]. Incidence of PMI varies depending on the diagnostic criteria and patient population [3,4]. Some studies report incidence rates up to 30%, though an average incidence of 3.9% established in a large systematic review seems more realistic [4]. The fourth universal definition of myocardial infarction (MI) arbitrarily defines a CABG-related PMI (Type 5) as elevation of cardiac troponin (cTn) values > 10 times the 99th percentile upper reference limit (URL) in patients with normal baseline values during the first 48 h following CABG surgery, combined with other clinical or echocardiographic evidence [5].

However, the current definition has its limitations. The diagnostic cutoff value of cTn > 10 × URL is arbitrarily defined and occurs in over 90% of all patients undergoing CABG surgery [1,6–8]. As a result,

Abbreviations: CABG, coronary artery bypass grafting; cTn, cardiac troponin; PMI, perioperative myocardial infarction; MI, myocardial infarction; URL, upper reference limit; OPCAB, off-pump coronary artery bypass grafting; LCMM, latent class linear mixed model; XC, aortic cross clamping; ECG, electrocardiogram; BIC, bayesian information criteria; PPV, positive predictive value; NPV, Negative predictive value; ICU, intensive care unit; LoS, length of stay; EHR, electronic health record

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https://doi.org/10.1016/j.cca.2020.01.025
Received 3 December 2019; Received in revised form 20 January 2020; Accepted 24 January 2020
Available online 27 January 2020
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even small degrees of myocardial damage may lead to additional di-
genostic procedures and subsequent clinical care pathways \[9\]. Alter-
natively, isolated elevations of cardiac biomarkers, which could be
prognostically signiﬁcant, are ignored in the absence of other evidence.

Several studies have focused on the release profile (or kinetics) of
cTn post-CABG, arguing that insight in the normal postoperative release
proﬁle can aid clinicians in recognizing patients with PMI and that
timing of the peak is relevant when applying cut-off values \[10\]-\[12\].
Aside from the normal post-operative CABG cTn release proﬁle, studies
describe proﬁles for off-pump CABG (OPCAB) surgery \[10,11,13\] and
surgeries complicated by PMI \[10-12,14-17\]. While these studies de-
 monstrate the variability in cTn release proﬁles and their value in rec-
ognizing PMI, they a posteriori deﬁne subgroups based on clinical char-
acteristics or outcomes and subsequently evaluate cTn proﬁles. An
alternative, assumption-free, approach is to group patients according
to cTn release proﬁles and a priori evaluate the clinical characteristics
and outcomes of each subgroup.

In this study we used an unsupervised statistical learning approach
to identify subgroups of patients without using any information other
than cTn release proﬁles post-CABG. To achieve this we used a sta-
tistical modeling technique called latent class linear mixed models
(LCMMs) \[18\].

Our ﬁrst aim was to ﬁt a LCMM to data from a cohort of CABG
patients where cTn was serially sampled post-operatively. From this
model, we investigated the mean cTn release proﬁles of the uncovered
classes and analyzed the subgroups of patients assigned to the classes
based on clinical characteristics and outcomes, including PMI. Finally,
the added value of the LCMM and serial cTn sampling in diagnosing
PMI was determined.

2. Materials and methods

2.1. Patient population

This study was a prospective observational cohort study and all
patients who underwent CABG surgery at the Catharina Hospital in
Eindhoven between February 2013 and February 2014 were included in
this study (N = 1028). Exclusion criteria were patients who underwent
CABG with concomitant surgery. If patients underwent a reoperation
during the inclusion period, only the ﬁrst operation was included in the
analysis. Blood samples for this study were residual samples obtained
during routine withdrawal. Primary endpoints were cTnT proﬁle after
uncomplicated cardiac surgery, cTnT proﬁle after cardiac surgery
complicated by PMI and short/long-term mortality. Patients with
missing data that had either (i) none or only one cTnT measurement
(N = 123), or (ii) where the aortic cross clamping (XC) time was not
registered (N = 4), were excluded. Patients were also excluded if there
was reasonable doubt whether the labeling of tubes was performed
correctly, i.e. a > 28 ng/L (≥ 2 × URL) decrease followed by > 28
ng/L increase during the ﬁrst 5 h post-CABG (N = 27).

2.2. cTnT measurements

Arterial blood samples were obtained preoperatively (≤ 2h before
surgery) and at 1.5 h, 2 h, 6 h and 12–24 h post XC. If the procedure
was performed as an OPCAB, the positioning of the mechanical stabi-
lization device was taken as reference point of time. Samples were
collected in BD Vacutainer® heparin tubes and immediately after
withdrawal assayed for cTnT concentration using a high-sensitive cTnT
Immunoassay from Roche Diagnostics Corporation on a Roche Elecsys®
platform. The Roche hs-cTnT assay has a 10% imprecision at 13 ng/L
with a 99th percentile URL of 14 ng/L.

2.3. PMI diagnosis

At the time this study was performed, diagnosis of PMI in our
institution was based on elevation of ASAT activity. PMI was registered
as a complication if ASAT activity was > 100 U/L combined with (1)
new Q waves on an electrocardiogram (ECG) or new left bundle branch
block; or (2) angiographic evidence of graft or native coronary artery
occlusion; or (3) echocardiographic imaging evidence of new regional
wall motion abnormality or new loss of viable myocardium.

2.4. Data collection and storage

Patient data was collected prospectively in the database of the de-
partment of cardiac surgery of our institution. These data included
demographic information, risk factors, and complications. cTnT results
were extracted from the laboratory information system. Mortality data
was obtained from the municipal personal records database. All study
data was merged and stored in a study database, see Appendix A for the
structure of the data.

2.5. Model ﬁtting

Linear mixed models \[19,20\] provide a ﬂexible method to analyze
longitudinal data since they incorporate between- and within-patient
variability, can handle irregularly sampled and missing data (under
the missing at random assumption). However, linear mixed models assume
that the underlying population is homogenous and can be described at
the population level by a unique proﬁle. If different subpopulations
exist within the total population, these have to be explicitly speciﬁed.
Latent class linear mixed models (LCMMs) assume that the population
is heterogeneous and composed of latent classes of subjects, char-
acterized by mean proﬁles of trajectories \[18,21\]. LCMMs are also re-
ferred to as growth mixture models. After the LCMM is ﬁtted, a post-
eriori classiﬁcation can be made which calculates the probability that
each subject belongs to each of the latent classes.

The LCMM consisted of a linear mixed model representing log10
transformed cTnT proﬁles over time and a multinomial logistic re-
gression model representing (latent) class membership. In the linear
mixed model the ﬁxed and random effects were modeled with natural
cubic splines since cTnT proﬁles were expected to be highly nonlinear.
Splines are preferred to polynomials due to their local nature and better
numerical properties \[22\]. No predictors were included in the multi-
nominal logistic regression model so class membership was not based on
any patient characteristics or outcomes. The LCMM was ﬁtted using R
version 3.6.1 \[23\] and the lcmm package version 1.8.1 \[18\]. A series of
LCMMs were ﬁtted, consisting of an increasing number of latent classes.
Since it is known that LCMMs can converge to local maxima \[18\], each
LCMM was ﬁtted 100 times with randomly chosen starting values to
ensure that each model converged to a global maximum. The number of
latent classes was increased until the Bayesian information criteria
(BIC) \[18,24\] started increasing with the addition of an extra latent
class. The selection of the best model was based on (i) the BIC and \(\Delta \text{BIC}\),
(ii) the posterior classiﬁcation table and (iii) clinical relevance \[18,25\].
Mathematical formulation, model selection procedures and R code used
to ﬁt the model can be found in Appendix A.

2.6. Post-hoc analysis

After selecting a LCMM, classes were given names based on the
volution of the mean cTnT. Class membership probabilities were cal-
culated and each patient was a posteriori assigned to the class that
corresponded to the highest probability. The differences between
classes were analyzed with respect to patient characteristics, procedural
characteristics and outcomes. If there were statistically signiﬁcant
\(p < 0.05\) differences between classes for a particular variable, post-
hoc tests were used to compare which particular pair(s) of classes dif-
ered. Tukey’s test was used for continuous variables, Dunn’s test for
non-normal continuous variables and pairwise Fisher tests for catego-
rical variables. The Holm-Bonferroni method was used to adjust p-
patients were assigned to a rising profile class (i.e. cTnT still rising at 24 h post XC) were considered positive for PMI by the LCMM. The classification of the LCMM was compared to the clinical diagnosis of PMI in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy using the caret package [26]. This was also done for the guideline definition [5] and for an optimally chosen cutoff. The optimally chosen cutoff was based on the Youden index [27] of the receiver operating characteristic (ROC) curve of the maximum cTnT value within 24 h post XC and the clinical diagnosis of PMI. Since a LCMM cannot be directly implemented in the clinic, we also assessed the added value of the LCMM in the clinical practice by defining a simple criterion based on visual inspection of the mean profiles.

3. Results

3.1. Study population

In total, 1028 patients were included in the study, see Fig. 1. Patients with concomitant procedures were excluded, leaving 778 patients that underwent CABG without combined surgery. Of these 778 patients, some patients had missing or incorrect data with respect to the cTnT measurements, the XC time or the labelling of pre- and post-operative samples. After excluding patients with missing or erroneous data, a total of 624 patients remained in the analysis. Patient characteristics and outcomes are summarized in Table 1.

3.2. Latent class mixed model

LCMMs were fitted with up to 6 latent classes. The BIC of the LCMMs decreased from 762.80 for a model without latent classes to a minimum of 514.86 for a model with 5 latent classes. The model with 4 latent classes (BIC = 518.86) was chosen as the final model, given the small decrease in BIC (-4.00) when going from 4 to 5 latent classes (reflecting modest evidence for a fifth class [28]) and higher discriminative ability. For more details regarding model selection, see Appendix A. In Fig. 2A the estimated mean profile of each of the four latent classes in the final model is plotted. Patients were assigned to the class with the highest posterior probability. The individual profiles of patients assigned to each of the four classes are shown in Fig. 2B. Classes were labelled according to the shape of the profile. The “normal profile” class (N = 523, 83.8%) contains the majority of patients and shows a typical cTnT profile post-CABG: a sharp increase in cTnT with a peak around 4 – 5 h post-XC, representing periprocedural myocardial damage, followed by a slow steady decline. The “rising profile” class (N = 29, 4.6%) shows an initial sharp increase similar to the “normal profile” but where the cTnT concentration continues to rise until the end of the measurement period (24 h). The “low profile” class (N = 40, 6.4%) shows a slower increase and a lower peak cTnT than the “normal profile”. The “high profile” class (N = 32, 5.1%) contains patients with an elevated baseline cTnT that peaks around 10 h post XC and then starts to decline.

3.3. Latent class characteristics and outcomes

Patients were assigned to the class with the highest posterior probability and classes were compared based on patient characteristics, procedural characteristics and outcomes in Table 2. Patients in the low profile class almost exclusively underwent OPCAB surgery and were on average younger than patients in the high profile class. Patients in the high or rising profile class had higher surgical risk (i.e. higher EuroSCORE) than patients in the normal or low profile class. This was also reflected by the fact that these patients more often underwent emergency procedures than patients in the normal profile class. Patients in the high or rising profile class had a longer length of stay (LoS) in the
intensive care unit (ICU) and hospital, than patients in the low or

Table 1
Characteristics of the study population and outcomes.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 624</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative</strong></td>
<td></td>
</tr>
<tr>
<td>Age in years †</td>
<td>65.65 (± 9.68)</td>
</tr>
<tr>
<td>Female gender</td>
<td>121 (19.4%)</td>
</tr>
<tr>
<td>Body mass index in kg/m² †</td>
<td>27.63 (± 4.01)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>134 (21.5%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>367 (58.8%)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>65 (10.4%)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>34 (5.4%)</td>
</tr>
<tr>
<td>Left-ventricular function</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>511 (81.9%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>90 (14.4%)</td>
</tr>
<tr>
<td>Poor</td>
<td>14 (2.2%)</td>
</tr>
<tr>
<td>Very poor</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (1.3%)</td>
</tr>
<tr>
<td>Additive EuroSCORE ‡</td>
<td>3.00 [2.00, 5.00]</td>
</tr>
<tr>
<td>Prior cardiac surgery</td>
<td>16 (2.6%)</td>
</tr>
<tr>
<td>Emergency procedure</td>
<td>16 (2.6%)</td>
</tr>
<tr>
<td>Pre-op hemoglobin (mmol/L) †</td>
<td>9.00 (± 0.88)</td>
</tr>
<tr>
<td>Pre-op creatinine (umol/L) ‡</td>
<td>88.00 [76.00, 100.00]</td>
</tr>
<tr>
<td><strong>Intraoperative</strong></td>
<td></td>
</tr>
<tr>
<td>Intra-aortic balloon pump</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>616 (98.7%)</td>
</tr>
<tr>
<td>Pre-op</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Per-op</td>
<td>3 (0.5%)</td>
</tr>
<tr>
<td>Post-op</td>
<td>3 (0.5%)</td>
</tr>
<tr>
<td>Off-pump CABG</td>
<td>133 (21.3%)</td>
</tr>
<tr>
<td>Aortic cross-clamp time (min.) ‡</td>
<td>45.00 [35.00, 59.00]</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time (min.) ‡</td>
<td>73.00 [57.00, 90.00]</td>
</tr>
<tr>
<td><strong>Postoperative</strong></td>
<td></td>
</tr>
<tr>
<td>Length of stay on ICU (days) ‡</td>
<td>1.00 [0.00, 1.00]</td>
</tr>
<tr>
<td>Length of stay in hospital (days) ‡</td>
<td>5.00 [4.00, 6.00]</td>
</tr>
<tr>
<td>Perioperative myocardial infarction</td>
<td>23 (3.7%)</td>
</tr>
<tr>
<td>Required reoperation</td>
<td>38 (6.1%)</td>
</tr>
<tr>
<td>Early mortality (30 days)</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>Late mortality (5 years)</td>
<td>49 (7.9%)</td>
</tr>
<tr>
<td>Number of cTnT measurements</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>29 (4.6%)</td>
</tr>
<tr>
<td>3</td>
<td>45 (7.2%)</td>
</tr>
<tr>
<td>4</td>
<td>121 (19.4%)</td>
</tr>
<tr>
<td>5</td>
<td>396 (63.5%)</td>
</tr>
<tr>
<td>6</td>
<td>31 (5.0%)</td>
</tr>
<tr>
<td>7</td>
<td>2 (0.3%)</td>
</tr>
</tbody>
</table>

CABG = coronary artery bypass grafting; ICU = intensive care unit; cTnT = cardiac troponin-T; † mean (± SD); ‡ median [IQR].

55% of patients in the rising profile class were clinically diagnosed with PMI whereas 98.8% of patients in any of the other classes were not clinically diagnosed with PMI. Patients that were assigned to the rising profile class were considered positive for PMI. Fig. 3 shows the agreement between the LCMM rising class PMI classification and the clinical diagnosis of PMI in our clinic. For 16 of the 23 patients that had PMI there is agreement between the LCMM and the clinical diagnosis (true/ concordant positives). 5 patients were classified in the normal profile class and 2 patients were classified in the high profile class, in spite of being clinically diagnosed with PMI (false/discordant negatives). 13 patients that were not clinically diagnosed with a PMI were classified in the rising profile class (false/discordant positives), the remaining 599 patients were all not diagnosed with a PMI and did not appear in the rising profile class (true/concordant negatives).

From the mean profiles in Fig. 2A it can be seen that only the PMI class is still rising between 6 and 24 h post XC. To assess the added value for the clinic, five different methods to classify patients with PMI are compared based on sensitivity, sensitivity, PPV, NPV and accuracy. The results are shown in Table 3. The LCMM approach had the highest accuracy and PPV without sacrificing NPV. The additional criterion that cTnT is rising between 6 and 24 h post XC improved accuracy compared to the current guideline criterion and an optimally chosen cut-off.

4. Discussion

In this study we investigated whether subgroups of patients could be identified based on cTnT release profiles post-CABG, in particular patients with PMI. Our results illustrate that by using a LCMM, subgroups of patients could be identified that show distinctive cTnT profiles without using any prior information other than serial cTnT measurements taken up to 24 h post XC. Using the model’s posterior classification of patients to a rising cTnT profile showed substantially greater accuracy and PPV (without affecting NPV) in diagnosing PMI compared to the guideline criteria.

First, a model with latent classes had a substantially lower BIC than a model without latent classes (518.86 versus 762.80), indicating that a model with latent classes is a better fit to the data [18,25,28]. In addition to the BIC, the diagonal terms in the posterior classification table were close to 1 (0.86, 0.89, 0.96, 0.94) reflecting good discriminative ability [18]. While the five class model had slightly lower BIC, the four class model was chosen due to the better discriminative ability. Also, there is substantive theory from literature which validates the choice for a four class model. The low profile class, which contains almost exclusively OPCAB surgeries, is in agreement with literature describing a delayed and lower peak for OPCAB surgery [10,11,13]. The rising profile class is also in agreement literature, describing a PMI profile as having a delayed peak or rise following an earlier peak [10,12,14–17]. To explain the cTnT release profile of patients with PMI, most studies refer to the work from Katus et. al who suggest that early release represents cytosolic troponin from myocytes that are reversible damaged, whereas late release (after one day) represents structural troponin from irreversibly damaged myocytes [29]. The high profile class is not described in literature. This is explained by the fact that most studies exclude patients with emergency procedures or procedures within seven days of a MI, which are most likely patients with elevated baseline cTnT in the high profile class.

The post hoc analysis revealed that the rising profile class consisted of more than half of patients clinically diagnosed with PMI.

There were thirteen discordant positive patients (of 624 in total), i.e. patients that were assigned to the rising profile class but were not clinically diagnosed with PMI. Nine patients had peak ASAT ≤ 100 U/l and did therefore not meet the ASAT-criterion to be diagnosed with PMI. The electronic health records (EHRs) of the remaining four patients were re-examined by a thoracic surgeon. Three patients had no secondary evidence (ECG or echocardiographic) of PMI and were therefore not diagnosed with PMI, one patient started to develop PMI but re-intervention took place before the final diagnosis was made.

There were seven discordant negative patients, i.e. patients that were clinically diagnosed with PMI but not assigned to the rising profile class. The EHRs of these seven patients were also re-examined by a thoracic surgeon. Five patients did not have elevated cardiac enzymes but were diagnosed with PMI on the basis of a combination of other diagnostic criteria i.e. ECG abnormalities, echocardiographic evidence or hemodynamic instability. Two patients were incorrectly clinically diagnosed with PMI, one patient had pre-operative MI and one patient was mislabeled as positive. Although only mismatched cases were re-examined, the causes of misclassification were mainly due to the ASAT criterion or (lack of) evidence of other clinical or echocardiographic abnormalities. If the two patients that were incorrectly labelled with PMI were re-classified as negative, the sensitivity of the LCMM increased to 0.76 and the specificity to 0.99.

That the LCMM is not in perfect agreement with the clinical diagnosis of PMI, is not merely a shortcoming of the model but also of the variation in the diagnosis of PMI. Confirming or denying a diagnosis of PMI may be of secondary importance to the clinical consequences. Although clinical consequences such as major adverse cardiac and cerebrovascular events were not registered in our study, post hoc tests revealed that patients with a rising cTnT profile had a longer LoS in the hospital (Dunn’s test p-value: 0.045), a longer LoS on the ICU (Dunn’s test p-value: 0.0036) and more often had signs of ischemia on an ECG (Fisher’s exact test p-value: < 0.001) than patients with a normal cTnT profile. This is in agreement with previous studies who reported associations between elevated post-operative cTnT and prolonged stay on the ICU\[30,31\].

A limitation of our study is that we did not have samples > 24 h post XC, therefore we could not determine the timing of the cTnT peak for patients with PMI. Previous studies observed a rising pattern even after 48 h \[11,14\]. However, non-PMI patients reach their peak between 4 and 12 h post XC, therefore 24 h is sufficient to distinguish early versus late peak occurrence. This finding also confirms the potential for early (< 12 h post-CABG) cTnT to detect patients at risk for PMI or other adverse events as reported by other studies \[31,32\].

Another limitation is that the model in its current form is difficult to implement in a prospective manner in the clinic. However, we have demonstrated that information gathered from the estimated mean cTnT profile (that cTnT in patients in the rising class is still rising between 6 and 24 h post XC) can already improve diagnostic accuracy, both with respect to the guideline and an optimally chosen cutoff. Our approach of visually interpreting estimated mean cTnT profiles does not take any

![Fig. 2. (A) Mean cTnT profiles of latent classes. Estimated mean profiles of log₁₀ cTnT in ng/L for each latent class from the final four class LCMM. (B) Individual cTnT profiles. Individual log₁₀ cTnT profiles of patients that were a posteriori assigned to one of the four latent classes. n is the number of patients a posteriori assigned to that class.](image)

Table 2

<table>
<thead>
<tr>
<th>Patient characteristics of latent classes.</th>
<th>Normal profile</th>
<th>High profile</th>
<th>Low profile</th>
<th>Rising profile</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 523</td>
<td>N = 32</td>
<td>N = 40</td>
<td>N = 29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years †</td>
<td>65.8 (± 9.4)</td>
<td>68.2 (± 10.6)</td>
<td>61.8 (± 12.1)</td>
<td>64.6 (± 8.9)</td>
<td>0.026</td>
</tr>
<tr>
<td>Female gender</td>
<td>97 (18.5%)</td>
<td>7 (21.9%)</td>
<td>9 (22.5%)</td>
<td>8 (27.6%)</td>
<td>0.602</td>
</tr>
<tr>
<td>EuroSCORE ‡</td>
<td>3.0 [2.0, 5.0]</td>
<td>6.0 [3.0, 7.0]</td>
<td>3.0 [1.0, 4.0]</td>
<td>3.0 [3.0, 5.0]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Emergency</td>
<td>5 (1.0%)</td>
<td>6 (18.8%)</td>
<td>2 (5.0%)</td>
<td>3 (10.3%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Off-pump CABG</td>
<td>81 (15.5%)</td>
<td>5 (15.6%)</td>
<td>38 (95.0%)</td>
<td>9 (31.0%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>XC time (min.) ‡</td>
<td>45.0 [35.0, 58.5]</td>
<td>49.0 [37.5, 58.5]</td>
<td>61.0 [60.5, 61.5]</td>
<td>59.0 [43.0, 64.2]</td>
<td>0.071</td>
</tr>
<tr>
<td>CPB time (min.) ‡</td>
<td>72.0 [55.0, 88.5]</td>
<td>77.5 [64.8, 80.0]</td>
<td>106.0 [102.5, 109.5]</td>
<td>94.0 [70.0, 99.0]</td>
<td>0.028</td>
</tr>
<tr>
<td>Days on ICU ‡</td>
<td>1.0 [0.0, 1.0]</td>
<td>1.0 [0.0, 2.0]</td>
<td>0.0 [0.0, 1.0]</td>
<td>2.0 [0.0, 3.0]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Days in hospital ‡</td>
<td>5.0 [4.0, 6.0]</td>
<td>6.0 [4.0, 9.0]</td>
<td>4.0 [4.0, 6.0]</td>
<td>6.0 [5.0, 7.0]</td>
<td>0.001</td>
</tr>
<tr>
<td>PMI</td>
<td>5 (1.0%)</td>
<td>2 (6.2%)</td>
<td>0 (0.0%)</td>
<td>16 (55.2%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ECG conclusion</td>
<td>440 (84.1%)</td>
<td>25 (78.1%)</td>
<td>33 (82.5%)</td>
<td>12 (41.4%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No ischemia</td>
<td>61 (11.7%)</td>
<td>6 (18.8%)</td>
<td>6 (15.0%)</td>
<td>7 (24.1%)</td>
<td></td>
</tr>
<tr>
<td>Possible ischemia</td>
<td>10 (1.9%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>10 (34.5%)</td>
<td></td>
</tr>
<tr>
<td>Definite ischemia</td>
<td>12 (2.3%)</td>
<td>1 (3.1%)</td>
<td>1 (2.5%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Inconclusive</td>
<td>4 (0.8%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0.855</td>
</tr>
<tr>
<td>Late mortality</td>
<td>41 (7.8%)</td>
<td>4 (12.5%)</td>
<td>3 (7.5%)</td>
<td>1 (3.4%)</td>
<td>0.628</td>
</tr>
</tbody>
</table>

χ² test for categorical variables, one-way ANOVA for normally distributed variables, Kruskal-Wallis rank sum test for non-normally distributed variables. † normal variables, mean (± SD) ‡ non-normal variables, median [IQR]. XC = aortic cross-clamp, CPB = cardiopulmonary bypass, ICU = intensive care unit, PMI = perioperative myocardial infarction.

*p-values determine if there are significant differences between classes.
Fig. 3. Confusion matrix plot. Individual log_{10} cTnT profiles of patients split by clinical diagnosis of PMI (upper row with clinical diagnosis of PMI, bottom row without PMI) and posterior class assignment by the LCMM (normal, high, low and rising profile in each column respectively). TP = true positives; FN = false negatives; FP = false positives; TN = true negatives.

Table 3
Sensitivity, specificity, PPV and NPV for different approaches to detecting patients with a PMI.

<table>
<thead>
<tr>
<th>cTnT PMI classification method</th>
<th>Sens.</th>
<th>Spec.</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guideline definition</td>
<td>0.96</td>
<td>0.18</td>
<td>0.05</td>
<td>0.99</td>
<td>0.21</td>
</tr>
<tr>
<td>Guideline definition &amp; rising after 6 h</td>
<td>0.91</td>
<td>0.40</td>
<td>0.06</td>
<td>0.99</td>
<td>0.42</td>
</tr>
<tr>
<td>Optimal cutoff &amp; rising after 6 h</td>
<td>0.91</td>
<td>0.83</td>
<td>0.18</td>
<td>1.00</td>
<td>0.83</td>
</tr>
<tr>
<td>LCMM rising class</td>
<td>0.87</td>
<td>0.87</td>
<td>0.22</td>
<td>0.99</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Sens. = sensitivity; Spec. = specificity; PPV = positive predictive value; NPV = negative predictive value; LCMM = latent class linear mixed model.

* The optimal cutoff for cTnT based on the Youden index was 528.9 ng/L.

variability into account and is only a proof of concept. Also, given the multifactorial causes for post-operative cTnT elevation, one can expect differences between centers. Consequently the results obtained from this single center analysis may not be generalizable to other centers.

Finally, although LCMMs do not prove that the found subpopulations actually exist [33] and skepticism of complex statistical models is appropriate, the fit indices combined with substantive theory and high diagnostic accuracy of PMI patients provide strong evidence to assume that the heterogeneity in cTnT release profiles is the result of actual subpopulations instead of other causes of non-normality. We have demonstrated that a statistical model is capable of recognizing clinically relevant subgroups of patients based on cTnT release profiles post-CABG and that information from this model can be used to improve the guideline for Type 5 MI. Future studies should be done to determine the optimal sampling time-points of cTnT to detect a rising pattern and the associated improvement compared to a single cut-off value in diagnosing PMI.

5. Conclusions

This study has shown that characteristic cTnT release profiles exist post-CABG surgery. These profiles could be uncovered by a LCMM without any prior information other than serial cTnT measurements up to 24 h post XC. Four classes were discovered that showed a low, high, rising and normal cTnT release profile. Patients were *posteriori* assigned to each of one of these classes. The rising profile proved to be predictive for PMI, with higher PPV and accuracy than the guideline recommended cutoff or an optimally chosen cutoff. We argue that a rising cTnT release profile is potentially of greater predictive value for PMI than a single value above or below a cutoff.

CRediT authorship contribution statement

Ruben Deneer: Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing - original draft, Visualization.

Astrid G.M. van Boxtel: Conceptualization, Investigation, Data curation, Writing - review & editing. Arjen-Kars Boer: Methodology, Writing - review & editing, Visualization, Supervision. Mohamed A. Soliman Hamad: Investigation, Writing - review & editing, Supervision. Natal A.W. van Riel: Methodology, Writing - review & editing, Supervision, Volkher Scharnhorst: Conceptualization, Resources, Writing - review & editing, Supervision, Project administration.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2020.01.025.

References


