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Clustering patients at the emergency department based on their ECG and PPG signals

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Abstract

Rationale Early diagnostics at the emergency department (ED) has several benefits, such as reduced mortality and improved patient satisfaction. Currently, electrocardiography (ECG) and photoplethysmography (PPG) are used to monitor patients in the ED. Studies have shown that machine learning models can determine various patient characteristics, such as age, gender and diabetes, based on their ECG or PPG signals, highlighting the potential that many more clinical parameters can be determined using these signals. This study aims to uncover which patient characteristics are most suitable to use in classification machine learning models to aid in early diagnostics.
Methods Patients enrolled in the Acutelines data-bio bank with ECG and PPG recordings available in the first half hour after admission to the ED were included in this study. The data was cleaned and a 30-second interval of clean data was selected for each patient. The dimensionality of these intervals was reduced using an autoencoder. Consequently, K-means multidimensional time series clustering was performed on the encoded representation of the features. How various patient characteristics were distributed over the clusters was analysed to determine which would have the most predictive value in a classification model.
Results In total, 1679 patient visits to the ED were clustered into four clusters. These clusters differed in baseline characteristics, such as age and comorbidities, but also in acute characteristics, such as vital parameters, SOFA score, and mortality. When validating the clusters using an additional 100 visits, age and heart rate were determined to be the most informative characteristics.
Conclusion When developing machine learning models based on ECG and PPG to aid in the diagnostics of patients at the ED, the parameters that should be focused on are mortality or ICU admission within 24 or 72 hours, blood levels of magnesium, CRP, glucose, NT-proBNP, troponin T, the likelihood and focus of an infection and SOFA score. It remains unclear, however, which aspects of the ECG and PPG signals specifically form the basis of this clustering.

1 Introduction

Emergency departments (EDs) around the world diagnose and treat many patients every day. In the Netherlands, 2.25 million people visited the EDs in 2019[1]. This is an increase compared to prior years, a trend which is expected to continue[2]. Combined with the shortage of healthcare workers, an increase of ED visits could cause problems such as crowding, which leads to decrease in quality of patient care, delays in treatment and worse adherence to guidelines. A British study by Jones et al. in 2022 concluded that wait times at the ED of 4-6 hours lead to an extra death in every 191 patients, while wait times of 6-8 hours lead to an extra death per 82 patients[3]. The chair of the Dutch association for ED doctors applied these results to waiting times at Dutch EDs, concluding that almost 1000 deaths are caused by long waiting times annually[4].

Early diagnostics reduce the time a patient spends at the ED, reducing mortality and morbidity and improving patient satisfaction[5]. Recently, many studies have been performed about early warning scores[6] and early diagnostics of specific diseases, such as sepsis[7]. Often, features such as vital parameters, lab values and demographics are used in these studies. Other readily available diagnostic tests, such as making an electrocardiogram (ECG) and monitoring vital parameters using photoplethysmography (PPG), are also used for early diagnostics. Recording these signals is inexpensive, non-invasive and provide healthcare professionals with a lot of information. Studies using these signals for early diagnostics often focus on cardiac conditions. However, recent studies have used machine learning to show that more information is present in these signals than meets the eye, such as age and gender[8, 9], diabetes[10], physical work capacity[11], atherosclerosis[12] and hypoglycemia[13]. These studies highlight the potential for the development of a tool using ECG and PPG signals for early diagnostics at the ED.

This study aims to discover additional patient parameters present in ECG and PPG signals by clustering patients at the ED based on their ECG and PPG signals recorded at triage using only unsupervised machine learning. Unsupervised machine learning seeks to find structure in unlabeled data[14]. Similar ECG and PPG signals are clustered together. If clinically relevant clusters are formed, this model can be used at triage to acquire additional information about the patient, thereby contributing to early diagnostics at the ED. Interesting characteristics could be mortality in the near future, certain diagnoses or an estimation of lab values. As age has been a prominent outcome in previous machine learning research for both ECG and PPG, age is expected to differ between the clusters here too. However, age is not expected to be the only difference between the clusters, allowing this model to contribute to early diagnostics.

2 Methods

For this study, data from the Acutelines data-bio bank was used. Acutelines is a multi-disciplinary prospective hospital-based cohort study which examines the complete acute patient journey admitted to the ED of the University Medical Centre Groningen (UMCG), a tertiary care teaching hospital in the Netherlands[15, 16]. It employs a broad range of investigative procedures in assessing the pre-hospital, in-hospital, and long-term health factors that affect outcomes in patients with acute conditions. The cohort population is broadly representative of the people living in the Northern Netherlands with acute medical conditions. Adult patients arriving at the ED for internal medicine, pulmonary medicine and acute medicine are included in Acutelines. Participants are asked for written informed consent, when applicable by proxy. The Acutelines cohort study is approved by the medical ethics committee of the UMCG and registered under trial registration number NCT04615065 at ClinicalTrials.gov[16].

All patients who visited the ED of the UMCG between September 2020 and June 2023 and who enrolled in Acutelines were included in this study. If a patient had no lead II ECG data or PPG data available in the first half hour after arrival at the ED, they were excluded from this study. For this specific study, ethical approval was obtained from the ethics committee of the UMCG (study number 16992).

Signal preprocessing
The first thirty minutes at the ED are often busy for a patient. A nurse will draw blood and take measurements, and the physicians talk with a patient and physically examine them. All necessary activities, but not helpful for making clean ECG and PPG recordings, as movement causes artifacts. ECGs were recorded with a frequency of 500Hz. The PPG signals were recorded at 250Hz. Prior to clustering, the signals were resampled to 100Hz and consequently cleaned using the neurokit method of the clean function of the python library NeuroKit2[17]. All programming and calculations were made using Python version 3.9.16 (Python Software Foundation, https://www.python.org/).

NeuroKit2 was also used to determine the signal quality of the ECG signals. Here, each sample of an ECG signal was given a score from 0 to 1 based on the correlation between the signal and an average ECG. Using a sliding window of 30 seconds starting every 0.5 seconds, the signal quality was calculated to find an interval with minimal artifacts. Sufficient signal quality for ECG was defined as at least 0.8 for 90% of the samples, without dropping below 0.65. If no sufficient interval was found, the signal was not used in further analysis.

The quality of the PPG signals was determined for the 30-second intervals for which the simultaneously measured ECG signal was of sufficient quality. To determine the quality of the PPG signals, the amplitude of the peaks was calculated for the normalised PPG signal. If the mean and standard deviation of the amplitudes of the peaks were in accordance with any of the below-mentioned criteria, the signal was deemed of sufficient quality for further analysis. These criteria were formulated by visually inspecting which signals were rejected by the criteria and adjusting the criteria until the signals with obvious insufficient quality were removed while preserving the signals which visually looked sufficient.

1. The mean amplitude of the peaks was greater than 0.51 while the standard deviation was less than 0.13
2. The mean amplitude of the peaks was greater than 0.6 while the standard deviation was less than 0.133
3. The mean amplitude of the peaks was greater than 0.7 while the standard deviation was less than 0.16

Finally, the number of heartbeats between the ECG and PPG intervals were compared. These should be the same for both signals, as they have been recorded simultaneously. Therefore, if the number of detected heartbeats differed more than one beat between the signals, the interval was deemed of insufficient quality. This mainly removed intervals in which either the ECG or PPG signal temporarily stopped recording, or where (movement) artefacts prevented accurate detection of the heartbeats. The first interval of 30 seconds for each patient which had sufficient quality in the first 30 minutes of recording was used in further analysis.

Autoencoder

Prior to clustering the ECG and PPG signals, their dimensionality needed to be reduced. Dimensionality reduction is a helpful step which emphasises the differences between the signals, enabling the clustering algorithm to produce better results[18]. A method to reduce dimensionality is by using an autoencoder[19]. Autoencoders are neural networks trained to reconstruct their input after summarising the input into latent variables. Autoencoders are often used as a model to generate new data, to further classify data in a semi-supervised setting, to detect anomalies, to denoise signals and to reduce dimensionality. Autoencoders have been used in the medical field with success, such as in the 2016 research by Wang et al. on the detection of microcalcifications on mammographies[20]. Although most medical research using autoencoder is done in the field of imaging, studies also use autoencoders on time series, mainly for the purposes of denoising and anomaly detection[21, 22, 23]. A few studies using autoencoders for dimensionality reduction of medical time series have been performed[24, 25]. Research suggests that using an autoencoder to perform dimensionality reduction provides better results than using principle component analysis, for example[19]. Figure 1 visualises the principle of an autoencoder.

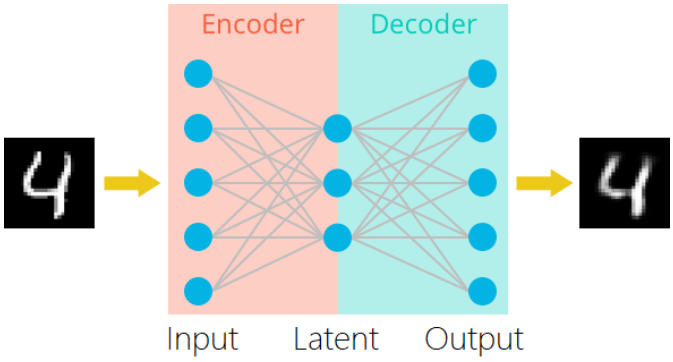

Figure 1: A simple representation of an auto-encoder. The input data is encoded and decoded such that the output optimally represents the input. Figure adapted from [26].

The autoencoder used in this study was the same as Thill et al. used in their 2021 paper on using an autoencoder for anomaly detection in time series[27]. They developed a temporal convolutional network autoencoder specifically for ECGs. The encoder consists of a stack of seven 1D convolutional layers. Each convolutional layer is followed by a 1 x 1 convolution. The outputs of these seven layers are concatenated and finally compressed by a factor 32 to their encoded representation (latent variables). The decoder follows these same steps in reverse order, making this autoencoder symmetrical. Additional settings used in the present study were a batch size of 32, and 100 epochs. The encoded representation of the signals was used in the clustering algorithm.

Clustering

The clustering algorithm K-Multi-Dimensional Time-Series Clustering (K-MDTSC), developed by Giordano et al., was used to cluster the data[28]. The encoded representation can be viewed as a time series, and having both ECG and PPG signals, makes the data multi-dimensional. K-MDTSC is based on the traditional K-means clustering method, where points are assigned to the closest centroid. The location of the centroids is then optimised by minimising the total sum of the distances between the points and their centroids. All points that share a centroid belong to the same cluster. 100 patients were kept out of the training of the clustering algorithm, to be used to verify the model. The number of clusters needs to be known upfront when applying K-means clustering. Therefore, the elbow method was used to determine which number of clusters from two to nine was best[29].

Homogeneity and completeness

After all signals were clustered, these clusters were analysed on homogeneity and completeness of numerous patient characteristics. If all the patients in a cluster share a characteristic, the cluster is homogeneous for that charac-

teristic. If all the patients that share a characteristic are in the same cluster, that cluster is complete for that characteristic[30]. A visualisation of homogeneity and completeness can be found in figure 2. If the clusters are homogeneous or complete for certain characteristics, then these characteristics can be used in supervised machine learning models with the goal of improving early diagnostics at the ED.

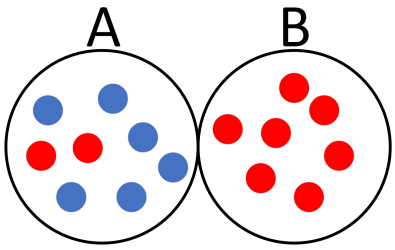

Figure 2: A visual representation of homogeneity and completeness. Group A is complete for the blue circles, as all the blue circles are in group A. Group B is homogeneous for the red circles, as it only contains red circles. Because group A contains red circles, group A is not homogeneous for blue, and group B is not complete for red.

Broadly, the characteristics analysed can be summarised into demographics, vital parameters, medication use, comorbidities, lab values, hospital admission and time to admission to the intensive care unit (ICU) or death. Statistical significance was calculated using the tableone library in python[31]. Their standard test for continuous non-normal variables is the Kruskul-Wallis test. For categorical variables, this is the chi-squared test. The tableone library automatically corrects for multiple testing by using the Bonferroni correction. Significance is defined as a p-value less than or equal to 0.05.

Searching for new features
To determine which elements of the ECG and PPG signals were informative to the model to base its clustering on, the difference of certain ECG and PPG features between the clusters were also analysed. These features were calculated per heartbeat in the analysed intervals and averaged per patient.

Verifying the new found features
The 100 visits kept aside to verify the model were assigned to the cluster with the closest centroid, calculated with the same distance metric as originally used to create the clusters. The patient characteristics of these clusters were also calculated and compared to the original clusters, to determine which patient characteristics were most important to the clustering algorithm.

3 Results

ECG and PPG recordings were started for 3951 patient visits in the first thirty minutes after arrival at the ED. 2296 visits had recordings of sufficient length to analyse further. Finally, after signal preprocessing, 1779 visits remained for the final analyses, of which 100 were kept aside. This is visualised in figure 3.

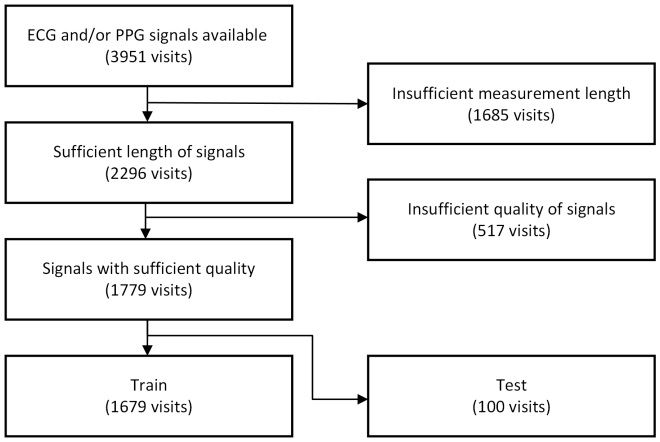

Figure 3: Total number of signals available for analysis

Figure 4 shows an example of a signal as original data and reconstructed after the autoencoder. The elbow plot, which depicts the total error per cluster, can be found in figure 5. The elbow plot does not show a clear optimal number of clusters. An argument could be made for both three and four clusters. For the remainder of this report, four clusters will be used as the optimal number of clusters.

How the most important patient characteristics are distributed over the four clusters can be found in Table 1. The sizes of the clusters vary, with cluster 1 containing 430 visits (25.61%), cluster 2 containing 388 visits (23.11%), cluster 3 containing 326 visits (19.41%) and cluster 4 containing 535 visits (31.86%). Though various characteristics differ significantly between the groups, none of the clusters can be seen as fully homogeneous or complete for these characteristics. Parameters differ in many of the categories of characteristics, such as baseline characteristics, vital parameters, blood values, outcomes and comorbidities. A full table with all characteristic compared can be found in Appendix A. Some of the variables in Table 1 are continuous. Box plots of some of the continuous variables which differ significantly between the clusters, can be found in Appendix B.

The ECG and PPG features calculated from their original signals can be found in Tables 2 and 3 respectively, along with their distribution over the clusters. Most of these features differ significantly between the clusters, failing to point to a limited number of features that can be seen as most discriminative for the clustering model.

The test set had few characteristics which differed significantly between the clusters, namely age, alcohol use, last smoke, heart rate, use of beta blockers, history of chronic pulmonary disease and diagnoses of fungal or parasitic infections. Only age, alcohol usage and heart rate are distributed over the clusters similarly to Table 1. The distribution of these six features can be found in Table 4. For the distribution of all patients characteristics over the test set can be found in Appendix C.

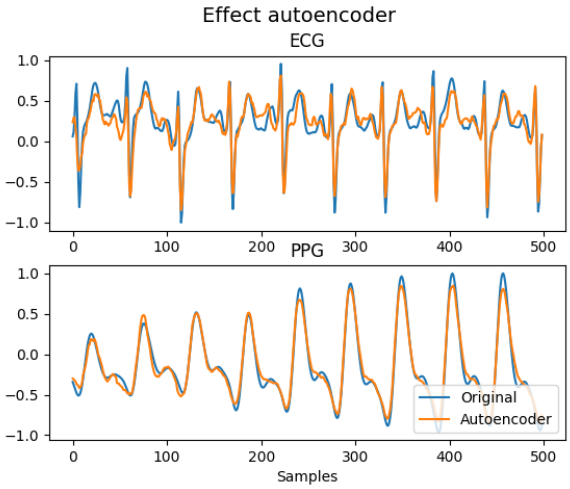

Figure 4: Original ECG and PPG signal (blue) compared to the output of the autoencoder (orange).

Figure 5: Sum of squared error of each point to the centre of its cluster for two to nine clusters. The optimal number of clusters is the number of clusters before the gradient stabilises. In this case, both 3 and 4 clusters could be seen as optimal. Four clusters will use used in the remainder of this report.

Table 1: Patient characteristics divided over the four clusters. P-values equal to or lower than 0.05 are highlighted in bold.

Characteristic		Missing	Overall	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P-Value
n (%)			1679	430 (25.61)	388 (23.11)	326 (19.41)	535 (31.86)	
Biological sex, n (%)	Female	0	751 (44.7)	168 (39.1)	165 (42.5)	165 (50.6)	253 (47.3)	**0.006**
	Male		928 (55.3)	262 (60.9)	223 (57.5)	161 (49.4)	282 (52.7)	
Age, median [Q1,Q3]		57	63.0 [50.0,73.0]	68.0 [58.0,76.0]	67.0 [56.0,75.0]	55.0 [41.0,66.0]	59.0 [44.0,72.0]	**<0.001**
Triage colour, n (%)		24						**0.002**
	Green		3 (0.2)	0 (0.0)	2 (0.5)	0 (0.0)	1 (0.2)	
	Yellow		1110 (67.1)	292 (68.9)	271 (70.9)	183 (56.8)	364 (69.1)	
	Orange		508 (30.7)	126 (29.7)	104 (27.2)	128 (39.8)	150 (28.5)	
	Red		34 (2.1)	6 (1.4)	5 (1.3)	11 (3.4)	12 (2.3)	
Transport method, n (%)		3						**0.001**
	Self		373 (22.3)	98 (22.8)	77 (19.9)	99 (30.5)	99 (18.5)	
	Ambulance		1288 (76.8)	331 (77.0)	305 (79.0)	220 (67.7)	432 (80.7)	
	Helicopter		8 (0.5)	0 (0.0)	3 (0.8)	2 (0.6)	3 (0.6)	
	Internal		7 (0.4)	1 (0.2)	1 (0.3)	4 (1.2)	1 (0.2)	
Admission to hospital, n (%)		1	1137 (67.8)	328 (76.3)	269 (69.3)	240 (73.8)	300 (56.1)	**<0.001**
Mortality, n (%)		0						
	Within 24 hours		16 (1.0)	4 (0.9)	6 (1.5)	6 (1.8)	0 (0.0)	**0.025**
	Within 48 hours		23 (1.4)	8 (1.9)	7 (1.8)	6 (1.8)	2 (0.4)	0.123
	Within 72 hours		31 (1.8)	8 (1.9)	8 (2.1)	10 (3.1)	5 (0.9)	0.155
	Within 30 days		139 (8.3)	43 (10.0)	39 (10.1)	22 (6.7)	35 (6.5)	0.093
Mortality or ICU admission, n (%)		0						
	Within 24 hours		119 (7.1)	29 (6.7)	21 (5.4)	36 (11.0)	33 (6.2)	**0.017**
	Within 48 hours		135 (8.0)	33 (7.7)	25 (6.4)	38 (11.7)	39 (7.3)	0.055
	Within 72 hours		143 (8.5)	34 (7.9)	26 (6.7)	41 (12.6)	42 (7.9)	**0.029**
Alcohol, n (%)		386	449 (34.7)	93 (27.4)	111 (37.4)	94 (37.2)	151 (37.4)	**0.013**
Smoker, past or present, n (%)		372	531 (40.6)	138 (39.9)	121 (40.2)	100 (39.7)	172 (42.2)	0.898
Last smoke, n (%)		1330*						**0.005**
	<2h		16 (4.6)	2 (2.1)	2 (2.4)	3 (5.0)	9 (8.3)	
	<1w		73 (20.9)	16 (16.8)	17 (20.0)	12 (20.0)	28 (25.7)	
	<3m		19 (5.4)	3 (3.2)	4 (4.7)	7 (11.7)	5 (4.6)	
	<1y		38 (10.9)	8 (8.4)	8 (9.4)	12 (20.0)	10 (9.2)	
	<10y		40 (11.5)	6 (6.3)	15 (17.6)	5 (8.3)	14 (12.8)	
	>10y		163 (46.7)	60 (63.2)	39 (45.9)	21 (35.0)	43 (39.4)	
Smoke years, median [Q1,Q3]		1280*	30.0 [16.0,45.0]	30.0 [20.0,45.0]	34.5 [20.0,50.0]	30.0 [10.0,36.0]	38.0 [15.0,45.0]	**0.038**
Drugs, n (%)		406	96 (7.5)	12 (3.6)	13 (4.5)	28 (11.1)	43 (10.8)	**<0.001**
Heart rate, median [Q1,Q3]		23	91.0 [77.0,105.0]	94.0 [76.0,108.0]	89.0 [77.0,98.0]	111.0 [102.0,120.0]	81.0 [70.0,91.0]	**<0.001**
SBP, median [Q1,Q3]		32	133.0 [117.0,150.0]	133.0 [120.0,151.5]	133.0 [115.0,150.0]	134.0 [119.0,148.0]	133.0 [116.8,151.0]	0.827
DBP, median [Q1,Q3]		32	79.0 [69.0,90.0]	79.0 [68.0,90.0]	77.0 [69.0,88.0]	81.0 [71.0,91.0]	79.0 [68.8,90.0]	**0.028**
MAP, median [Q1,Q3]		32	97.3 [86.7,108.8]	97.0 [86.5,108.5]	95.3 [85.3,108.0]	98.3 [88.2,110.0]	97.7 [86.7,108.3]	0.298
Respiratory rate, median [Q1,Q3]		239	19.0 [16.0,23.0]	20.0 [17.0,24.0]	19.0 [16.0,23.2]	20.0 [17.0,24.0]	18.0 [15.0,21.0]	**<0.001**
Temperature, median [Q1,Q3]		164	36.8 [36.5,37.4]	36.9 [36.5,37.6]	36.9 [36.5,37.4]	37.0 [36.6,37.8]	36.7 [36.3,37.2]	**<0.001**
SpO2, median [Q1,Q3]		30	97.0 [95.0,99.0]	97.0 [94.0,98.0]	97.0 [94.0,98.0]	97.0 [95.0,98.0]	98.0 [96.0,99.0]	**<0.001**

*patients who do not smoke are included in the missing values

Characteristic		Missing	Overall	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P-Value
Method of oxygen, n (%)		69						**0.031**
	Room air		1228 (76.3)	302 (72.4)	277 (75.9)	228 (72.6)	421 (81.9)	
	Nasal cannula		297 (18.4)	90 (21.6)	70 (19.2)	64 (20.4)	73 (14.2)	
	NIV		14 (0.9)	1 (0.2)	3 (0.8)	5 (1.6)	5 (1.0)	
	Non-rebreathing		55 (3.4)	15 (3.6)	12 (3.3)	14 (4.5)	14 (2.7)	
	Venti mask		9 (0.6)	5 (1.2)	2 (0.5)	2 (0.6)	0 (0.0)	
	Larynx mask		7 (0.4)	4 (1.0)	1 (0.3)	1 (0.3)	1 (0.2)	
Blood values, median [Q1,Q3]								
	Magnesium	447	0.8 [0.7,0.9]	0.8 [0.7,0.9]	0.8 [0.7,0.9]	0.8 [0.7,0.8]	0.8 [0.7,0.9]	**0.001**
	CRP	38	17.0 [3.1,81.0]	23.0 [6.0,95.0]	23.5 [3.8,88.8]	42.0 [7.0,113.5]	7.0 [1.6,37.5]	**<0.001**
	Glucose	60	6.7 [5.8,8.4]	7.0 [5.9,9.0]	6.7 [5.8,8.0]	7.1 [6.0,8.8]	6.3 [5.5,7.8]	**<0.001**
	NT-proBNP	767	300.5 [84.0,1267.2]	501.0 [140.2,2609.2]	296.5 [89.8,1444.0]	202.0 [65.0,989.0]	187.0 [55.5,781.0]	**<0.001**
	Troponin T	710	16.0 [8.0,34.0]	22.0 [12.0,43.0]	18.0 [9.0,40.0]	15.0 [8.0,35.5]	12.0 [7.0,22.0]	**<0.001**
Medication, n (%)		0						
	Betablockers		390 (23.2)	126 (29.3)	108 (27.8)	53 (16.3)	103 (19.3)	**<0.001**
	Antiarrythmics		23 (1.4)	12 (2.8)	4 (1.0)	3 (0.9)	4 (0.7)	**0.032**
	Diuretics		350 (20.8)	123 (28.6)	91 (23.5)	45 (13.8)	91 (17.0)	**<0.001**
Charlson comorbidity index, n (%)		0						
	Myocardial infarction		106 (6.3)	43 (10.0)	28 (7.2)	7 (2.1)	28 (5.2)	**<0.001**
	Heart failure		115 (6.8)	50 (11.6)	23 (5.9)	11 (3.4)	31 (5.8)	**<0.001**
	Peripheral vascular disease		78 (4.6)	30 (7.0)	12 (3.1)	15 (4.6)	21 (3.9)	**0.046**
	Chronic pulmonary disease		338 (20.1)	114 (26.5)	82 (21.1)	52 (16.0)	90 (16.8)	**<0.001**
	Diabetes without complications		227 (13.5)	74 (17.2)	59 (15.2)	32 (9.8)	62 (11.6)	**0.009**
	Diabetes with organ damage		67 (4.0)	24 (5.6)	21 (5.4)	9 (2.8)	13 (2.4)	**0.023**
	Severe kidney disease		116 (6.9)	42 (9.8)	32 (8.2)	15 (4.6)	27 (5.0)	**0.007**
	Lymphoma or multiple myeloma		75 (4.5)	32 (7.4)	12 (3.1)	18 (5.5)	13 (2.4)	**0.001**
	Metastasised solid tumor		151 (9.0)	51 (11.9)	28 (7.2)	42 (12.9)	30 (5.6)	**<0.001**
CCI: total score, median [Q1,Q3]		0	3.0 [1.0,5.0]	4.0 [3.0,6.0]	3.0 [2.0,6.0]	2.0 [1.0,5.0]	3.0 [1.0,5.0]	**<0.001**
Other comorbidities		0						
	Hypertension		373 (22.2)	109 (25.3)	96 (24.7)	49 (15.0)	119 (22.2)	**0.003**
	PCI or CABG		101 (6.0)	39 (9.1)	30 (7.7)	7 (2.1)	25 (4.7)	**<0.001**
Organ transplants, n (%)								
	Number of transplants	0						**0.002**
	0		1572 (93.6)	390 (90.7)	355 (91.5)	318 (97.5)	509 (95.1)	
	1		88 (5.2)	33 (7.7)	26 (6.7)	8 (2.5)	21 (3.9)	
	2		19 (1.1)	7 (1.6)	7 (1.8)	0 (0.0)	5 (0.9)	
	Stem cell	0	30 (1.8)	15 (3.5)	6 (1.5)	5 (1.5)	4 (0.7)	**0.014**
Aortic and cardiac surgeries, n (%)		0						**0.002**
	1		88 (5.2)	33 (7.7)	26 (6.7)	8 (2.5)	21 (3.9)	
	2		19 (1.1)	7 (1.6)	7 (1.8)	0 (0.0)	5 (0.9)	
Infections, n(%)		0						
	Total		758 (45.1)	225 (52.3)	186 (47.9)	188 (57.7)	159 (29.7)	**<0.001**
	Bacterial		537 (32.0)	164 (38.1)	133 (34.3)	140 (42.9)	100 (18.7)	**<0.001**
	Viral		365 (21.7)	101 (23.5)	99 (25.5)	81 (24.8)	84 (15.7)	**<0.001**
	Fungal or parasitic		33 (2.0)	5 (1.2)	10 (2.6)	12 (3.7)	6 (1.1)	**0.027**
	Enteritis		269 (16.0)	81 (18.8)	76 (19.6)	57 (17.5)	55 (10.3)	**<0.001**
	Lower respiratory tract		384 (22.9)	105 (24.4)	108 (27.8)	89 (27.3)	82 (15.3)	**<0.001**
	Urinary tract		188 (11.2)	61 (14.2)	47 (12.1)	41 (12.6)	39 (7.3)	**0.005**
	Cholangitis		11 (0.7)	7 (1.6)	3 (0.8)	0 (0.0)	1 (0.2)	**0.016**
Department, n(%)		2						
	Acute medicine		516 (30.8)	100 (23.0)	106 (27.3)	77 (23.6)	233 (43.6)	**<0.001**
	Pulmonology		387 (23.1)	108 (25.1)	101 (26.0)	79 (24.2)	99 (18.5)	**0.024**
	Oncology		94 (5.6)	33 (7.7)	13 (3.4)	29 (8.9)	19 (3.6)	**<0.001**

Characteristic		Missing	Overall	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P-Value
Diagnoses, based on IDC-10 codes, n(%)		0						
	Infections (A-B)		201 (12.0)	60 (14.0)	41 (10.6)	51 (15.6)	49 (9.2)	**0.015**
	Other bacterial diseases (A30-49)		91 (5.4)	32 (7.4)	19 (4.9)	24 (7.4)	16 (3.0)	**0.007**
	Neoplasms (C-D48)		111 (6.6)	27 (6.3)	23 (5.9)	36 (11.0)	25 (4.7)	**0.003**
	Malignant neoplasms of unspecified sites (C76-80)		24 (1.5)	4 (1.4)	4 (1.0)	12 (3.7)	4 (0.7)	**0.002**
	Metabolic disorders (E70-90)		130 (7.7)	37 (8.6)	28 (7.2)	35 (10.7)	30 (5.6)	**0.044**
	Delirium (F05)		38 (10.9)	5 (1.2)	17 (4.4)	7 (2.1)	9 (1.7)	**0.011**
	Diseases of the circulatory system (I)		255 (15.2)	74 (17.2)	50 (12.9)	39 (12.0)	92 (17.2)	0.064
	Diseases of the respiratory system (J)		433 (25.8)	127 (29.5)	118 (30.4)	88 (27.0)	100 (18.7)	**<0.001**
	Diseases of the genitourinary system (N)		208 (12.4)	58 (13.5)	58 (14.9)	43 (13.2)	49 (9.2)	**0.043**
	Tachycardia (R00.0)		13 (0.8)	2 (0.5)	1 (0.3)	9 (2.8)	1 (0.2)	**<0.001**
	Pain in throat and chest (R07)		82 (4.9)	14 (3.3)	19 (4.9)	9 (2.8)	40 (7.5)	**0.004**
	Other symptoms and signs involving the circulatory and respiratory systems (R09)		30 (1.8)	9 (2.1)	7 (1.8)	11 (3.4)	3 (0.6)	**0.023**
	Asphyxia (R09.0)		23 (1.4)	7 (1.6)	6 (1.5)	9 (2.8)	1 (0.2)	**0.015**
	Fever of other and unknown origin (R50)		80 (4.8)	23 (5.3)	15 (3.9)	33 (10.1)	9 (1.7)	**<0.001**
	Syncope and collapse (R55)		100 (6.0)	20 (4.7)	25 (6.4)	6 (1.8)	49 (9.2)	**<0.001**
	Injury, poisoning and certain other consequences of external causes (S-T)		142 (8.5)	23 (5.3)	28 (7.2)	35 (10.7)	56 (10.5)	**0.011**
	Injury of unspecified region (T14)		30 (1.8)	4 (0.9)	2 (0.5)	6 (1.8)	18 (3.4)	**0.005**
	Poisoning by drugs, medicaments and biological substances (T36-50)		43 (2.6)	4 (0.9)	5 (1.3)	12 (3.7)	22 (4.1)	**0.003**
Highest SOFA first 24 hours, n(%)		0						
	0-1		742 (44.4)	154 (35.8)	164 (42.4)	131 (40.6)	293 (55.0)	**<0.001**
	2-5		809 (48.4)	241 (56.0)	199 (51.4)	163 (50.5)	206 (38.6)	**<0.001**
	6-9		105 (6.3)	33 (7.7)	20 (5.2)	25 (7.7)	27 (5.1)	0.192
	10+		13 (0.8)	0 (0.0)	4 (1.0)	3 (0.9)	6 (1.1)	0.201
Signal quality, n(%)		1483						0.454
	Good		118 (60.2)	30 (62.5)	27 (60.0)	19 (55.9)	42 (60.9)	
	Sufficient		62 (31.6)	15 (31.2)	11 (24.4)	12 (35.3)	24 (34.8)	
	Insufficient		16 (8.2)	3 (6.2)	7 (15.6)	3 (8.8)	3 (4.3)	

Table 2: ECG features divided over the four clusters. P-values equal to or lower than 0.05 are highlighted in bold.

ECG feature, median [Q1,Q3]	Missing	Overall	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P-Value
Heart rate	2	90.1 [75.9,102.9]	91.2 [75.1,105.1]	86.8 [75.1,96.4]	109.7 [102.1,119.5]	80.1 [70.9,90.2]	**<0.001**
Heart rate variability (SDNN)	45	17.0 [8.9,36.8]	14.9 [8.0,42.4]	23.1 [11.7,51.2]	9.0 [6.1,14.9]	22.6 [13.3,39.5]	**<0.001**
QTc	615	411.8 [389.2,439.2]	425.9 [394.7,460.3]	409.8 [390.4,441.6]	397.1 [374.8,413.8]	414.0 [391.6,433.8]	**<0.001**
PR interval	360	146.4 [133.6,162.3]	145.5 [134.7,163.2]	146.8 [134.3,163.5]	145.6 [131.2,159.6]	147.3 [133.3,163.8]	0.395
QRS width	860	159.8 [135.6,183.0]	158.2 [138.0,180.2]	156.1 [130.6,176.2]	170.6 [137.4,203.8]	161.3 [136.2,188.3]	**0.007**
T wave width	18	134.4 [111.0,150.4]	134.7 [112.5,150.9]	134.3 [110.0,149.4]	122.0 [98.6,141.3]	139.5 [122.7,153.6]	**<0.001**
Height R peak	2	734.9 [609.2,818.2]	655.4 [474.5,782.7]	701.0 [551.5,786.4]	745.0 [656.2,809.0]	788.1 [702.3,846.1]	**<0.001**
Height P top	4	-198.4 [-439.0,96.4]	306.9 [188.8,455.7]	-98.0 [-184.5,3.4]	-302.4 [-416.8,-190.3]	-494.7 [-595.2,-396.0]	**<0.001**
Height T top	20	-42.4 [-334.7,286.9]	542.0 [334.7,778.6]	45.9 [-67.2,211.8]	-283.1 [-439.8,-83.7]	-349.9 [-494.8,-150.2]	**<0.001**

Table 3: PPG features divided over the four clusters. P-values equal to or lower than 0.05 are highlighted in bold.

PPG feature, median [Q1,Q3]	Missing	Overall	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P-Value
Height midpoint systolic increase	19	44.7 [8.2,96.0]	46.1 [5.8,94.4]	45.9 [10.0,108.4]	28.2 [1.8,72.1]	54.1 [12.4,105.8]	**<0.001**
Height systolic peak	19	744.2 [705.4,800.1]	743.8 [703.1,794.2]	742.2 [705.3,800.2]	739.6 [707.8,783.0]	749.6 [707.2,813.5]	0.196
Height diastolic peak	266	-77.6 [-281.5,112.4]	-69.5 [-267.4,134.2]	-63.3 [-274.6,125.3]	-218.5 [-364.8,-52.0]	3.5 [-196.1,165.0]	**<0.001**
Greatest systolic slope	266	149.4 [125.7,169.2]	146.7 [123.1,163.4]	141.6 [121.5,159.3]	166.6 [153.2,179.4]	140.2 [117.9,163.6]	**<0.001**
Greatest diastolic slope	1636	-15.6 [-22.1,-11.2]	-19.4 [-22.4,-8.9]	-16.9 [-22.3,-13.8]	3.2 [3.2,3.2]	-14.2 [-21.7,-11.4]	0.342
Greatest systolic acceleration	19	24.5 (7.4)	23.6 (7.2)	22.9 (7.0)	29.8 (5.9)	23.0 (7.2)	**<0.001**
Greatest negative acceleration	19	-21.4 [-28.7,-15.1]	-20.9 [-27.4,-14.3]	-19.2 [-24.8,-14.0]	-29.8 [-34.7,-24.1]	-18.7 [-25.5,-13.3]	**<0.001**
Greatest diastolic acceleration	266	6.4 [4.4,9.3]	6.3 [4.3,8.8]	5.7 [4.2,8.0]	9.6 [6.8,12.2]	5.7 [3.9,7.9]	**<0.001**

Table 4: Characteristics which differ significantly between clusters in the test set.

Characteristic		Missing	Overall	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P-Value
n			100	21	18	16	45	
Age, median [Q1,Q3]		3	66 [51,74]	69 [65,76]	70 [51,75]	50 [34,62]	65 [43,74]	**0.003**
Alcohol, n (%)		16	27 (32.1)	0 (0.0)	6 (40.0)	6 (42.9)	15 (40.5)	**0.012**
Last smoke, n (%)		75*						**0.020**
	<2h		2 (8.0)	2 (20.0)	2 (2.4)	2 (20.0)	9 (8.3)	
	<1w		4 (16.0)	0 (0.0)	3 (75.0)	0 (0.0)	1 (9.1)	
	<3m		2 (8.0)	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	
	<1y		2 (8.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (18.2)	
	<10y		2 (8.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (18.8)	
	>10y		13 (52.0)	4 (80.0)	1 (25.0)	2 (40.0)	6 (54.5)	
Heart rate, median [Q1,Q3]		0	88.0 [76.0,98.2]	91.0 [76.0,102.0]	89.0 [79.2,99.0]	107.5 [98.0,117.8]	82.0 [73.0,89.0]	**<0.001**
Use of beta blockers, n(%)		0	31 (31.0)	8 (38.1)	5 (27.8)	0 (0.0)	18 (40.0)	**0.024**
Chronic pulmonary disease, n (%)		0	21 (21.0)	9 (42.9)	3 (16.7)	4 (25.0)	5 (11.1)	**0.029**
Fungal or parasitic infection		0	2 (2.0)	0 (0.0)	0 (0.0)	2 (12.5)	0 (0.0)	**0.013**

*patients who do not smoke are included in the missing values

4 Discussion

This study aimed to uncover which patient characteristics can be determined from ECG and PPG signals using clustering. In the end, four clusters were found. Although no homogeneity or completeness was discovered, many characteristics differed significantly between the clusters. For these characteristics, supervised classification models can be developed. By using ECG and PPG signals for the classification of these characteristics instead of their traditional diagnostic methods, diagnostics at the ED could be accelerated.

The formed clusters can be described as follows. Cluster 1 consists of more elderly patients with cardiac conditions. This is mainly based on the characteristics 'age', 'NT-proBNP', 'troponin T' and the Charlson comorbidities. Furthermore, the SOFA score is highest in this group in the first 24 hours. Cluster 2 resembles cluster 1. However, the patients in cluster 2 have a lower illness severity, as can be seen in the fewer hospital admissions. The focus of disease is also slightly more pulmonary compared to cluster 1, shown by the number of patients admitted for pulmonology and patients diagnosed with a pulmonary condition. Interestingly, cluster 2 also contains most cases of delirium. Cluster 3 describes the younger patients who are more severely ill. The vital parameters of these patients deviate most from normal and they have the highest mortality and ICU admissions. Furthermore, these patients are diagnosed most often with infection, neoplasms and metabolic disorders. The final cluster, cluster 4, on the other hand, contains the patients who are least severely ill, having no mortality within the first 24 hours and having the lowest SOFA score in the first 24 hours. The vital parameters of these patients deviate least from normal, and these patients are least often diagnosed with an infection. Furthermore, the patients in cluster 4 are most likely to be admitted for acute medicine, instead of a more specific specialism. The diagnoses that occur more in cluster 4 compared to the other clusters are pain in throat and chest, syncope or collapse, injury and poisoning.

Another interesting detail appears when comparing the distribution of mortality between the clusters with the distribution of the SOFA score. As patients with a higher SOFA score are at a higher risk of mortality[32], it would be expected that the cluster with the lowest SOFA score has the lowest mortality. Cluster 4 follows this hypothesis. However, cluster 1 has the highest SOFA score, while cluster 3 has the highest mortality in the first 24 hours. This could suggest that ECG and PPG signals hold information that can predict mortality more accurately than the SOFA score. This hypothesis would need to be investigated in further research, however, to determine whether this finding is not simply caused by the low mortality in 24 hours. Furthermore, the SOFA score was originally developed for use at the ICU, and the measurements here are done at the ED.

As can be seen in Tables 2 and 3, the clusters also differ from each other in the ECG and PPG features. If only a few of these differences would have been significant, it would be easier to point at a specific part of the signals on which the clustering algorithm based its clustering. To uncover which ECG and PPG features are informative, a logistic regression analysis could be performed, using the ECG and PPG features as input data, training the model to predict the cluster and testing this on the 100 patients kept out of the clustering model. However, the method of calculating the ECG and PPG features required cleaner signals than the ones available, leading to a lot of missing data. Due to the missing data, this analysis could not be performed. Using better methods to calculate these features could be helpful in determining on which parts of the ECG and PPG signals the clustering model is based.

When comparing the distribution of characteristics in Table 1 to the clusters in Table 4, the clusters in Table 4 are less clear to define. Age and heart rate are distributed similarly to Table 1 while also being significantly different between the clusters. It could be concluded that these two variables are most important in defining the clusters. That age is an important factor of ECG and PPG signals is in accordance with literature[8, 9]. Other variables that differ significantly in Table 4 do not resemble the division in Table 1 at all. This can be seen in the use of beta blockers, for example, where 19.3% of patients in cluster 4 use beta blockers in the train data, while 40% use beta blockers in the validation set. For variables such as these, it can be concluded that the model has not clustered based on differences in ECG and PPG caused by these variables. To be able to better differentiate

the important variables from the less important variables, this study could be repeated by using a larger validation set. Preferably, an external dataset would be used to determine whether similar clusters are formed, similar to the 2021 study by Zweck et al[33].

A strength of this study was the use of an autoencoder for dimensionality reduction of the ECG and PPG signals. Each patient had 3000 samples of ECG and 3000 samples of PPG data, which the autoencoder summarised in 93 variables each; a compression factor of 32. Although the autoencoder did not perfectly recreate the original signals, as can be seen in figure 4, the autoencoder was able to follow the the variations in the signals for the most part, as can be seen in the PPG signal, where the variations in amplitude were followed well.

To improve the model, more focus should be placed on the pre-processing of the data. After pre-processing, approximately 200 signals were visually inspected, of which 8.2% were deemed of insufficient quality. More extensive and precise methods of signal pre-processing could have been used[34]. However, the aim of this research was to use clustering to determine for which patient characteristics future machine learning models should be developed. Due to time limitations, less time was spent on signal pre-processing than what would have been desirable. However, if more research will be done with these signals, it would be a worthwhile time investment to pre-process them well, as better input gives better output in machine learning. On the other hand, the artefacts in the signals most likely did not influence the clustering too much, as the signals deemed of insufficient quality were not all grouped in the same cluster. An advantage of better pre-processing could also be a decrease in the number of signals excluded from the signals due to insufficient quality. Excluding these patients may have introduced a form of bias, as it is possible that a portion of these patients had poor signal quality due to being more ill and nurses and doctors performing more medical treatments in the first half hour after arrival at the ED.

Another form of bias can be found in which patients were monitored using ECG and PPG in the first place. Although these tests are routine at the ED, not all patients require monitoring. Possibly, patients with less severe illness were not monitored using these tests, or monitoring started later than the first half hour after admission to the ED. If the patients excluded due to insufficient signal quality and absence of monitoring could have been included, the differences between the clusters might have been larger, as the differences in disease severity might have been greater. Including these patients would also give a better representation of a final model. If this model were to be implemented and used on all patients, patients would be asked to be still for the duration of the measurement, leading to signals of higher quality, and therefore to fewer exclusions.

Although the general description of each of the clusters fits with the results presented in Table 1, it remains unclear which characteristics are significant due to correlations with other characteristics. As mentioned above, age is known to affect ECGs. The question arises whether the number of transplants, for example, also alters the signals. As transplants are typically done at an older age, this variable could only be significantly different due to age being significantly different. When taking the interquartile ranges of distributions of age into account, it becomes apparent that the model has not solely clustered based on age, as the overlap in age between the groups is large.

As heart rate is another important characteristic which differs between the groups both in the original clusters and in the validation set, it may be interesting to determine how well these clusters can be replicated based on age and heart rate alone. Which other characteristics lie at the core of this division, needs to be further researched, possibly using a multivariate regression model. Another possibility is analysing individual patients. Some patients visited the ED multiple times. It could be interesting to see whether all instances of this patient arriving at the ED are clustered in the same cluster. If the problem for which a patient arrived at the ED differed per visit and the visits are clustered in different clusters, then the clusters probably reflect changes in the signals due to acute conditions rather than pre-existing comorbidities. Analysing the individual patients may also help to pinpoint individual characteristics that could explain why these patients are grouped together.

The results of this study contribute to the development of faster diagnoses for patients at the ED by identifying which patient characteristics have potential to develop a supervised machine learning model for. These characteristics are, for example, mortality or ICU admission within 24 or 72 hours, blood levels of magnesium, CRP, glucose, NT-proBNP and troponin T, and the likelihood and focus of an infection. Perhaps even the SOFA score could be predicted from ECG and PPG signals. The SOFA score is used to predict organ failure from a variety of clinical parameters. Some of these parameters are blood values. Predictions of the SOFA using ECG and PPG would be faster than waiting for the blood results. If would also be interesting to compare a model predicting mortality using ECG and PPG signals to the SOFA score, as the cluster with higher SOFA scores did not have the highest mortality. Estimations of the NT-proBNP and troponin T could be a beneficial feature immediately, as they are not always determined initially with the rest of the blood work, but are requested later when the relevance arises. Estimations from ECG and PPG could therefore remove the need to wait for these lab requests. What the focus of an infection is, or the type of microorganism caused it, could be helpful when a patient is septic and in need of quick treatment when the official diagnosis through a urine test, nasal swab, blood culture or scan is not yet known. Further research will have to show whether these characteristics can indeed be determined accurately from ECG and PPG signals.

To conclude, when clustering ECG and PPG data, four clusters came forward, varying mainly in age, heart rate and disease severity. Some characteristics were identified for which the development of a supervised machine learning model has potential. Next, research should focus on developing supervised machine learning models with these characteristics as outcomes, to be used to aid early diagnostics at the ED.

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Appendix A

Table 5: All patient characteristics of the train set divided over the four clusters. P-values equal to or lower than 0.05 are highlighted in bold. *patients who do not smoke are included in the missing values

Characteristic		Missing	Overall	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P-Value
n (%)			1679	430 (25.61)	388 (23.11)	326 (19.41)	535 (31.86)	
Biological sex, n (%)	Female	0	751 (44.7)	168 (39.1)	165 (42.5)	165 (50.6)	253 (47.3)	**0.006**
	Male		928 (55.3)	262 (60.9)	223 (57.5)	161 (49.4)	282 (52.7)	
Age, median [Q1,Q3]		57	63.0 [50.0,73.0]	68.0 [58.0,76.0]	67.0 [56.0,75.0]	55.0 [41.0,66.0]	59.0 [44.0,72.0]	**<0.001**
Height, median [Q1,Q3]		1266	175.0 [168.0,182.0]	175.5 [168.0,180.2]	174.0 [167.0,182.0]	175.0 [168.0,183.2]	175.0 [168.0,184.0]	0.908
Weight, median [Q1,Q3]		1264	80.0 [69.5,92.0]	80.0 [70.0,91.2]	80.0 [70.0,93.0]	79.0 [63.0,95.0]	78.0 [68.8,89.2]	0.794
BMI, median [Q1,Q3]		1267	26.0 [23.0,29.0]	26.0 [24.0,29.0]	27.0 [24.0,30.0]	25.0 [22.0,29.0]	25.0 [22.2,28.0]	0.292
Triage colour, n (%)		24						**0.002**
	Green		3 (0.2)	0 (0.0)	2 (0.5)	0 (0.0)	1 (0.2)	
	Yellow		1110 (67.1)	292 (68.9)	271 (70.9)	183 (56.8)	364 (69.1)	
	Orange		508 (30.7)	126 (29.7)	104 (27.2)	128 (39.8)	150 (28.5)	
	Red		34 (2.1)	6 (1.4)	5 (1.3)	11 (3.4)	12 (2.3)	
Transport method, n (%)		3						**0.001**
	Self		373 (22.3)	98 (22.8)	77 (19.9)	99 (30.5)	99 (18.5)	
	Ambulance		1288 (76.8)	331 (77.0)	305 (79.0)	220 (67.7)	432 (80.7)	
	Helicopter		8 (0.5)	0 (0.0)	3 (0.8)	2 (0.6)	3 (0.6)	
	Internal		7 (0.4)	1 (0.2)	1 (0.3)	4 (1.2)	1 (0.2)	
Ambulance urgency, n (%)		511						0.086
	A1		248 (21.2)	58 (19.8)	48 (17.2)	58 (28.7)	84 (21.3)	
	A2		893 (76.5)	228 (77.8)	222 (79.6)	141 (69.8)	302 (76.6)	
	B		27 (2.3)	7 (2.4)	9 (3.2)	3 (1.5)	8 (2.0)	
Admission to hospital, n (%)		1	1137 (67.8)	328 (76.3)	269 (69.3)	240 (73.8)	300 (56.1)	**<0.001**
Length of stay (h), median [Q1,Q3]		567	100.0 [47.8,194.4]	110.3 [47.6,211.4]	96.1 [54.9,168.0]	111.3 [56.4,228.7]	92.1 [41.8,185.2]	0.118
Mortality, n (%)								
	Within 24 hours	0	16 (1.0)	4 (0.9)	6 (1.5)	6 (1.8)	0 (0.0)	**0.025**
	Within 48 hours	0	23 (1.4)	8 (1.9)	7 (1.8)	6 (1.8)	2 (0.4)	0.123
	Within 72 hours	0	31 (1.8)	8 (1.9)	8 (2.1)	10 (3.1)	5 (0.9)	0.155
	Within 30 days	0	139 (8.3)	43 (10.0)	39 (10.1)	22 (6.7)	35 (6.5)	0.093
ICU admission, n (%)								
	Within 24 hours	0	109 (6.5)	27 (6.3)	18 (4.6)	31 (9.5)	33 (6.2)	
	Within 48 hours	0	118 (7.0)	27 (6.3)	21 (5.4)	33 (10.1)	37 (6.9)	0.082
	Within 72 hours	0	119 (7.1)	28 (6.5)	21 (5.4)	33 (10.1)	37 (6.9)	0.091
Mortality or ICU admission, n (%)								
	Within 24 hours	0	119 (7.1)	29 (6.7)	21 (5.4)	36 (11.0)	33 (6.2)	**0.017**
	Within 48 hours	0	135 (8.0)	33 (7.7)	25 (6.4)	38 (11.7)	39 (7.3)	0.055
	Within 72 hours	0	143 (8.5)	34 (7.9)	26 (6.7)	41 (12.6)	42 (7.9)	**0.029**
Alcohol, n (%)		386	449 (34.7)	93 (27.4)	111 (37.4)	94 (37.2)	151 (37.4)	**0.013**
Smoker, past or present, n (%)		372	531 (40.6)	138 (39.9)	121 (40.2)	100 (39.7)	172 (42.2)	0.898
Last smoke, n (%)		1330*						**0.005**
	<2h		16 (4.6)	2 (2.1)	2 (2.4)	3 (5.0)	9 (8.3)	
	<1w		73 (20.9)	16 (16.8)	17 (20.0)	12 (20.0)	28 (25.7)	
	<3m		19 (5.4)	3 (3.2)	4 (4.7)	7 (11.7)	5 (4.6)	
	<1y		38 (10.9)	8 (8.4)	8 (9.4)	12 (20.0)	10 (9.2)	
	<10y		40 (11.5)	6 (6.3)	15 (17.6)	5 (8.3)	14 (12.8)	
	>10y		163 (46.7)	60 (63.2)	39 (45.9)	21 (35.0)	43 (39.4)	

Characteristic		Missing	Overall	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P-Value
Smoke years, median [Q1,Q3]		1280*	30.0 [16.0,45.0]	30.0 [20.0,45.0]	34.5 [20.0,50.0]	30.0 [10.0,36.0]	38.0 [15.0,45.0]	**0.038**
Pack years, median [Q1,Q3]		0	0.0 [0.0,0.0]	0.0 [0.0,0.0]	0.0 [0.0,0.0]	0.0 [0.0,0.0]	0.0 [0.0,0.0]	0.833
Drugs, n (%)		406	96 (7.5)	12 (3.6)	13 (4.5)	28 (11.1)	43 (10.8)	**<0.001**
Heart rate, median [Q1,Q3]		23	91.0 [77.0,105.0]	94.0 [76.0,108.0]	89.0 [77.0,98.0]	111.0 [102.0,120.0]	81.0 [70.0,91.0]	**<0.001**
SBP, median [Q1,Q3]		32	133.0 [117.0,150.0]	133.0 [120.0,151.5]	133.0 [115.0,150.0]	134.0 [119.0,148.0]	133.0 [116.8,151.0]	0.827
DBP, median [Q1,Q3]		32	79.0 [69.0,90.0]	79.0 [68.0,90.0]	77.0 [69.0,88.0]	81.0 [71.0,91.0]	79.0 [68.8,90.0]	**0.028**
MAP, median [Q1,Q3]		32	97.3 [86.7,108.8]	97.0 [86.5,108.5]	95.3 [85.3,108.0]	98.3 [88.2,110.0]	97.7 [86.7,108.3]	0.298
Respiratory rate, median [Q1,Q3]		239	19.0 [16.0,23.0]	20.0 [17.0,24.0]	19.0 [16.0,23.2]	20.0 [17.0,24.0]	18.0 [15.0,21.0]	**<0.001**
Temperature, median [Q1,Q3]		164	36.8 [36.5,37.4]	36.9 [36.5,37.6]	36.9 [36.5,37.4]	37.0 [36.6,37.8]	36.7 [36.3,37.2]	**<0.001**
SpO2, median [Q1,Q3]		30	97.0 [95.0,99.0]	97.0 [94.0,98.0]	97.0 [94.0,98.0]	97.0 [95.0,98.0]	98.0 [96.0,99.0]	**<0.001**
Method of oxygen, n (%)		69						**0.031**
	Room air		1228 (76.3)	302 (72.4)	277 (75.9)	228 (72.6)	421 (81.9)	
	Nasal cannula		297 (18.4)	90 (21.6)	70 (19.2)	64 (20.4)	73 (14.2)	
	NIV		14 (0.9)	1 (0.2)	3 (0.8)	5 (1.6)	5 (1.0)	
	Non-rebreathing		55 (3.4)	15 (3.6)	12 (3.3)	14 (4.5)	14 (2.7)	
	Venti mask		9 (0.6)	5 (1.2)	2 (0.5)	2 (0.6)		
	Larynx mask		7 (0.4)	4 (1.0)	1 (0.3)	1 (0.3)	1 (0.2)	
O2 liters, median [Q1,Q3]		1390	3 [2,4]	3 [2,4]	3 [2,4]	2 [2,4]	3 [2,4]	0.139
GCS: total, median [Q1,Q3]		55	15 [15,15]	15 [15,15]	15 [15,15]	15 [15,15]	15 [15,15]	0.905
GCS: Eyes, n (%)		52						0.544
	1		40 (2.5)	7 (1.7)	7 (1.9)	11 (3.5)	15 (2.9)	
	2		8 (0.5)	2 (0.5)	2 (0.5)	2 (0.6)	2 (0.4)	
	3		82 (5.0)	25 (6.0)	22 (5.9)	9 (2.8)	26 (5.0)	
	4		1497 (92.0)	382 (91.8)	344 (91.7)	295 (93.1)	476 (91.7)	
GCS: Motor, n (%)		54						0.385
	1		23 (1.4)	1 (0.2)	5 (1.3)	7 (2.2)	10 (1.9)	
	2		1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	
	3		1 (0.1)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	
	4		8 (0.5)	2 (0.5)	1 (0.3)	1 (0.3)	4 (0.8)	
	5		30 (1.8)	10 (2.4)	6 (1.6)	5 (1.6)	9 (1.7)	
	6		1562 (96.1)	401 (96.6)	363 (96.8)	302 (95.6)	496 (95.6)	
GCS: Verbal, n (%)		51						0.204
	Intubated		10 (0.6)	1 (0.2)	1 (0.3)	2 (0.6)	6 (1.2)	
	1		32 (2.0)	4 (1.0)	6 (1.6)	11 (3.5)	11 (2.1)	
	2		12 (0.7)	2 (0.5)	4 (1.1)	2 (0.6)	4 (0.8)	
	3		24 (1.5)	10 (2.4)	3 (0.8)	4 (1.3)	7 (1.3)	
	4		82 (5.0)	16 (3.8)	26 (6.9)	16 (5.0)	24 (4.6)	
	5		1468 (90.2)	383 (92.1)	335 (89.3)	283 (89.0)	467 (90.0)	
Blood values, median [Q1,Q3]								
	Sodium	25	137 [134,140]	137 [134,139]	137 [134, 140]	137 [134, 139]	138 [136,140]	**<0.001**
	Potassium	38	4.1 [3.8,4.4]	4.1 [3.7,4.4]	4.1 [3.8,4.5]	4.0 [3.7,4.4]	4.0 [3.8,4.4]	0.151
	Magnesium	447	0.8 [0.7,0.9]	0.8 [0.7,0.9]	0.8 [0.7,0.9]	0.8 [0.7,0.8]	0.8 [0.7,0.9]	**0.001**
	Calcium	140	2.3 [2.2,2.4]	2.3 [2.2,2.4]	2.3 [2.2,2.4]	2.3 [2.2,2.4]	2.3 [2.2,2.4]	0.567
	Creatinin	38	81 [64,111]	84 [63,120]	86 [66,118]	76 [62,105]	79 [64,99]	**0.005**
	CRP	38	17.0 [3.1,81.0]	23.0 [6.0,95.0]	23.5 [3.8,88.8]	42.0 [7.0,113.5]	7.0 [1.6,37.5]	**<0.001**
	Leukocyts	55	9.2 [6.8,12.8]	9.3 [6.7,12.4]	9.2 [7.0,12.7]	9.6 [7.1,14.0]	9.0 [6.6,12.2]	0.083
	Glucose	60	6.7 [5.8,8.4]	7.0 [5.9,9.0]	6.7 [5.8,8.0]	7.1 [6.0,8.8]	6.3 [5.5,7.8]	**<0.001**
	NT-proBNP	767	300.5 [84.0,1267.2]	501.0 [140.2,2609.2]	296.5 [89.8,1444.0]	202.0 [65.0,989.0]	187.0 [55.5,781.0]	**<0.001**
	Troponin T	710	16.0 [8.0,34.0]	22.0 [12.0,43.0]	18.0 [9.0,40.0]	15.0 [8.0,35.5]	12.0 [7.0,22.0]	**<0.001**
	Lactate	147	1.3 [0.9,2.0]	1.3 [1.0,2.0]	1.2 [0.9,1.9]	1.5 [1.0,2.2]	1.3 [0.9,1.9]	0.001
Medication, n (%)								
	Betablockers		390 (23.2)	126 (29.3)	108 (27.8)	53 (16.3)	103 (19.3)	**<0.001**
	TCA		66 (3.9)	15 (3.5)	14 (3.6)	18 (5.5)	19 (3.6)	0.437
	Antiarrythmics		23 (1.4)	12 (2.8)	4 (1.0)	3 (0.9)	4 (0.7)	**0.032**
	Digoxin		32 (1.9)	12 (2.8)	9 (2.3)	4 (1.2)	7 (1.3)	0.264
	Diuretics		350 (20.8)	123 (28.6)	91 (23.5)	45 (13.8)	91 (17.0)	**<0.001**

Characteristic		Missing	Overall	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P-Value
Charlson comorbidity index, n (%)								
	Myocardial infarction	0	106 (6.3)	43 (10.0)	28 (7.2)	7 (2.1)	28 (5.2)	**<0.001**
	Heart failure	0	115 (6.8)	50 (11.6)	23 (5.9)	11 (3.4)	31 (5.8)	**<0.001**
	Peripheral vascular disease	0	78 (4.6)	30 (7.0)	12 (3.1)	15 (4.6)	21 (3.9)	**0.046**
	CVA or TIA	0	152 (9.1)	49 (11.4)	39 (10.1)	19 (5.8)	45 (8.4)	0.052
	Dementia	0	11 (0.7)	4 (0.9)	4 (1.0)		3 (0.6)	0.312
	Chronic pulmonary disease	0	338 (20.1)	114 (26.5)	82 (21.1)	52 (16.0)	90 (16.8)	**<0.001**
	Connective tissue disease	0	39 (2.3)	11 (2.6)	8 (2.1)	12 (3.7)	8 (1.5)	0.214
	Peptic ulcer disease	0	16 (1.0)	2 (0.5)	4 (1.0)	4 (1.2)	6 (1.1)	0.675
	Mild liver disease	0	32 (1.9)	8 (1.9)	6 (1.5)	8 (2.5)	10 (1.9)	0
	Diabetes without complications	0	227 (13.5)	74 (17.2)	59 (15.2)	32 (9.8)	62 (11.6)	**0.009**
	Diabetes with organ damage	0	67 (4.0)	24 (5.6)	21 (5.4)	9 (2.8)	13 (2.4)	**0.023**
	Hemiplegia	0	10 (0.6)	1 (0.2)	4 (1.0)	2 (0.6)	3 (0.6)	0.530
	Severe kidney disease	0	116 (6.9)	42 (9.8)	32 (8.2)	15 (4.6)	27 (5.0)	**0.007**
	Solid tumor without metastases	0	182 (10.8)	53 (12.3)	47 (12.1)	32 (9.8)	50 (9.3)	0.359
	Leukemia	0	34 (2.0)	8 (1.9)	7 (1.8)	9 (2.8)	10 (1.9)	0.775
	Lymphoma or multiple myeloma	0	75 (4.5)	32 (7.4)	12 (3.1)	18 (5.5)	13 (2.4)	**0.001**
	Severe liver disease	0	34 (2.0)	8 (1.9)	8 (2.1)	4 (1.2)	14 (2.6)	0.562
	Metastasised solid tumor	0	151 (9.0)	51 (11.9)	28 (7.2)	42 (12.9)	30 (5.6)	**<0.001**
	AIDS	0	3 (0.2)	2 (0.5)			1 (0.2)	0.354
CCI: total score, median [Q1,Q3]		0	3.0 [1.0,5.0]	4.0 [3.0,6.0]	3.0 [2.0,6.0]	2.0 [1.0,5.0]	3.0 [1.0,5.0]	**<0.001**
Other comorbidities								
	Pregnancy	0	2 (0.1)		1 (0.3)		1 (0.2)	0.629
	Hypertension	0	373 (22.2)	109 (25.3)	96 (24.7)	49 (15.0)	119 (22.2)	**0.003**
	Hypercholesterolemia	0	80 (4.8)	20 (4.7)	22 (5.7)	11 (3.4)	27 (5.0)	0.533
	PCI or CABG	0	101 (6.0)	39 (9.1)	30 (7.7)	7 (2.1)	25 (4.7)	**<0.001**
	Heart valve replacement	0	16 (1.0)	4 (0.9)	6 (1.5)	1 (0.3)	5 (0.9)	0.408
Organ transplantations, n (%)								
	Number of transplants	0						**0.002**
	0		1572 (93.6)	390 (90.7)	355 (91.5)	318 (97.5)	509 (95.1)	
	1		88 (5.2)	33 (7.7)	26 (6.7)	8 (2.5)	21 (3.9)	
	2		19 (1.1)	7 (1.6)	7 (1.8)		5 (0.9)	
	Kidney	0	73 (4.3)	19 (4.4)	20 (5.2)	12 (3.7)	22 (4.1)	0.793
	Heart	0	6 (0.4)	3 (0.7)	3 (0.8)	0 (0.0)	0 (0.0)	0.095
	Lung	0	21 (1.3)	1 (0.2)	8 (2.1)	5 (1.5)	7 (1.3)	0.116
	Liver	0	23 (1.4)	9 (2.1)	6 (1.5)	2 (0.6)	6 (1.1)	0.337
	Pancreas	0	1 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 0.344
	Tissue	0	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0.544
	Stem cell	0	30 (1.8)	15 (3.5)	6 (1.5)	5 (1.5)	4 (0.7)	**0.014**
Aortic surgeries, n (%)	1	0	5 (0.3)	3 (0.7)	1 (0.3)	0 (0.0)	1 (0.2)	0.317
Cardiac surgeries, n (%)		0						**0.004**
	1		87 (5.2)	32 (7.4)	25 (6.4)	8 (2.5)	22 (4.1)	
	2		17 (1.0)	6 (1.4)	7 (1.8)	0 (0.0)	4 (0.7)	
Aortic and cardiac surgeries, n (%)		0						**0.002**
	1		88 (5.2)	33 (7.7)	26 (6.7)	8 (2.5)	21 (3.9)	
	2		19 (1.1)	7 (1.6)	7 (1.8)	0 (0.0)	5 (0.9)	

Characteristic	Missing	Overall	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P-Value
Infections, n(%)	0						
Total		758 (45.1)	225 (52.3)	186 (47.9)	188 (57.7)	159 (29.7)	**<0.001**
Bacterial		537 (32.0)	164 (38.1)	133 (34.3)	140 (42.9)	100 (18.7)	**<0.001**
Viral		365 (21.7)	101 (23.5)	99 (25.5)	81 (24.8)	84 (15.7)	**<0.001**
Fungal or parasitic		33 (2.0)	5 (1.2)	10 (2.6)	12 (3.7)	6 (1.1)	**0.027**
Central nervous system		4 (0.2)	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.4)	0.231
Enteritis		269 (16.0)	81 (18.8)	76 (19.6)	57 (17.5)	55 (10.3)	**<0.001**
Lower respiratory tract		384 (22.9)	105 (24.4)	108 (27.8)	89 (27.3)	82 (15.3)	**<0.001**
Abdominal		59 (3.5)	20 (4.7)	10 (2.6)	16 (4.9)	13 (2.4)	0.095
Bone or joint		5 (0.3)	2 (0.5)	0 (0.0)	3 (0.9)	0 (0.0)	0.060
Gastrointestinal		57 (3.4)	12 (2.8)	14 (3.6)	16 (4.9)	15 (2.8)	0.337
Urinary tract		188 (11.2)	61 (14.2)	47 (12.1)	41 (12.6)	39 (7.3)	**0.005**
Skin or soft tissue		32 (1.9)	12 (2.8)	3 (0.8)	9 (2.8)	8 (1.5)	0.101
Other		43 (2.6)	11 (2.6)	9 (2.3)	14 (4.3)	9 (1.7)	0.129
Pericarditis		8 (0.5)	1 (0.2)	0 (0.0)	3 (0.9)	4 (0.7)	0.205
Endocarditis		5 (0.3)	0 (0.0)	1 (0.3)	2 (0.6)	2 (0.4)	0.475
Peritonitis		2 (0.1)	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0.470
Cholangitis		11 (0.7)	7 (1.6)	3 (0.8)	0 (0.0)	1 (0.2)	**0.016**
Cholecystitis		4 (0.2)	1 (0.2)	1 (0.3)	1 (0.3)	1 (0.2)	0.988
Pancreatitis		1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0.544
Diagnoses, based on IDC-10 codes, n(%)	0						
Infections (A-B)		201 (12.0)	60 (14.0)	41 (10.6)	51 (15.6)	49 (9.2)	**0.015**
Other bacterial diseases (A30-49)		91 (5.4)	32 (7.4)	19 (4.9)	24 (7.4)	16 (3.0)	**0.007**
Neoplasms (C-D48)		111 (6.6)	27 (6.3)	23 (5.9)	36 (11.0)	25 (4.7)	**0.003**
Malignant neoplasms of unspecified sites (C76-80)		24 (1.5)	4 (1.4)	4 (1.0)	12 (3.7)	4 (0.7)	**0.002**
Endocrine, nutritional and metabolic diseases (E)		193 (11.5)	55 (12.8)	40 (10.3)	45 (13.8)	53 (9.9)	0.233
Metabolic disorders (E70-90)		130 (7.7)	37 (8.6)	28 (7.2)	35 (10.7)	30 (5.6)	**0.044**
Mental and behavioural disorders (F)		139 (8.3)	23 (5.3)	34 (8.8)	30 (9.2)	52 (9.7)	0.078
Delirium (F05)		38 (10.9)	5 (1.2)	17 (4.4)	7 (2.1)	9 (1.7)	**0.011**
Behavioural syndromes associated with physiological disturbances and physical factors (F50-59)		4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.7)	**0.036**
Diseases of the circulatory system (I)		255 (15.2)	74 (17.2)	50 (12.9)	39 (12.0)	92 (17.2)	0.064
Diseases of the respiratory system (J)		433 (25.8)	127 (29.5)	118 (30.4)	88 (27.0)	100 (18.7)	**<0.001**
Diseases of the digestive system (K)		221 (13.2)	67 (15.6)	39 (10.1)	40 (12.3)	75 (14.0)	0.109
Diseases of the skin and subcutaneous tissue (L)		26 (1.5)	6 (1.4)	7 (1.8)	5 (1.5)	8 (1.5)	0.97
Diseases of the musculoskeletal system and connective tissue (M)		56 (3.3)	14 (3.3)	14 (3.6)	7 (2.1)	21 (3.9)	0.551
Diseases of the genitourinary system (N)		208 (12.4)	58 (13.5)	58 (14.9)	43 (13.2)	49 (9.2)	**0.043**
Symptoms, signs and abnormal clinical and laboratory findings not classified elsewhere (R)		654 (39.0)	156 (36.3)	148 (38.1)	125 (38.3)	225 (42.1)	0.306
Tachycardia (R00.0)		13 (0.8)	2 (0.5)	1 (0.3)	9 (2.8)	1 (0.2)	**<0.001**
Pain in throat and chest (R07)		82 (4.9)	14 (3.3)	19 (4.9)	9 (2.8)	40 (7.5)	**0.004**
Other symptoms and signs involving the circulatory and respiratory systems (R09)		30 (1.8)	9 (2.1)	7 (1.8)	11 (3.4)	3 (0.6)	**0.023**
Asphyxia (R09.0)		23 (1.4)	7 (1.6)	6 (1.5)	9 (2.8)	1 (0.2)	**0.015**
Fever of other and unknown origin (R50)		80 (4.8)	23 (5.3)	15 (3.9)	33 (10.1)	9 (1.7)	**<0.001**
Syncope and collapse (R55)		100 (6.0)	20 (4.7)	25 (6.4)	6 (1.8)	49 (9.2)	**<0.001**
Injury, poisoning and certain other consequences of external causes (S-T)		142 (8.5)	23 (5.3)	28 (7.2)	35 (10.7)	56 (10.5)	**0.011**
Injury of unspecified region (T14)		30 (1.8)	4 (0.9)	2 (0.5)	6 (1.8)	18 (3.4)	**0.005**
Poisoning by drugs, medicaments and biological substances (T36-50)		43 (2.6)	4 (0.9)	5 (1.3)	12 (3.7)	22 (4.1)	**0.003**
External causes of morbidity and mortality (V-Y)		4 (0.2)	2 (0.5)	2 (0.5)	0 (0.0)	0 (0.0)	0.236

Characteristic		Missing	Overall	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P-Value
Signal quality, n(%)		1483						0.454
	Good		118 (60.2)	30 (62.5)	27 (60.0)	19 (55.9)	42 (60.9)	
	Sufficient		62 (31.6)	15 (31.2)	11 (24.4)	12 (35.3)	24 (34.8)	
	Insufficient		16 (8.2)	3 (6.2)	7 (15.6)	3 (8.8)	3 (4.3)	
Department, n(%)		2						
	Acute medicine		516 (30.8)	100 (23.0)	106 (27.3)	77 (23.6)	233 (43.6)	**<0.001**
	Pulmonology		387 (23.1)	108 (25.1)	101 (26.0)	79 (24.2)	99 (18.5)	**0.024**
	Internal medicine		337 (20.1)	87 (20.2)	92 (23.7)	67 (20.6)	91 (17.0)	0.094
	Gastroenterology		131 (7.8)	39 (9.1)	27 (7.0)	30 (9.2)	35 (6.6)	0.332
	Hematology		111 (6.6)	35 (8.1)	22 (5.7)	27 (8.3)	27 (5.1)	0.123
	Oncology		94 (5.6)	33 (7.7)	13 (3.4)	29 (8.9)	19 (3.6)	**<0.001**
	Nephrology		65 (3.9)	17 (4.0)	17 (4.4)	11 (3.4)	20 (3.7)	0.914
	Reumatology		14 (0.8)	4 (0.9)	2 (0.5)	4 (1.2)	4 (0.7)	0.757
	Urology		12 (0.7)	5 (1.2)	3 (0.8)	1 (0.3)	3 (0.6)	0.536
	Geriatry		10 (0.6)	2 (0.5)	4 (1.0)	1 (0.3)	3 (0.6)	0.607
Highest SOFA first 24 hours		0						
	0-1		742 (44.4)	154 (35.8)	164 (42.4)	131 (40.6)	293 (55.0)	**<0.001**
	2-5		809 (48.4)	241 (56.0)	199 (51.4)	163 (50.5)	206 (38.6)	**<0.001**
	6-9		105 (6.3)	33 (7.7)	20 (5.2)	25 (7.7)	27 (5.1)	0.192
	10+		13 (0.8)	0 (0.0)	4 (1.0)	3 (0.9)	6 (1.1)	0.201

Appendix B

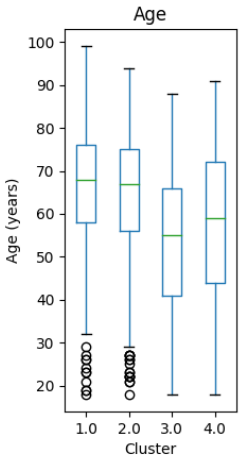

Figure 6: Division of age

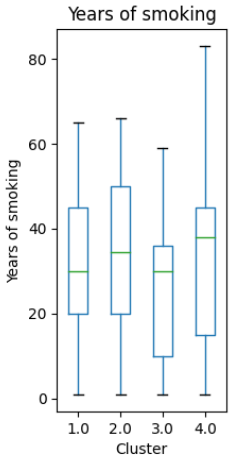

Figure 7: Division of smoke years

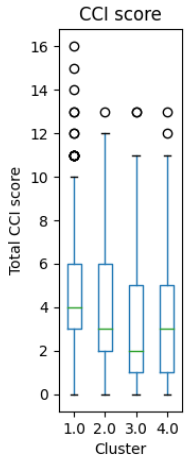

Figure 8: Division of CCI

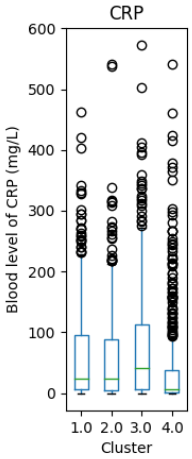

Figure 9: Division of CRP

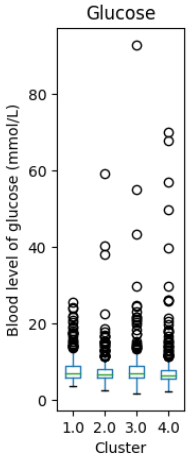

Figure 10: Division of glucose

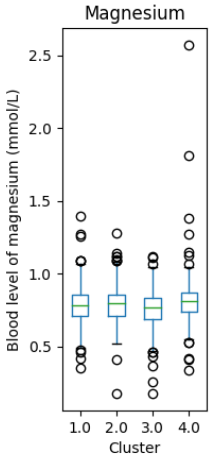

Figure 11: Division of magnesium

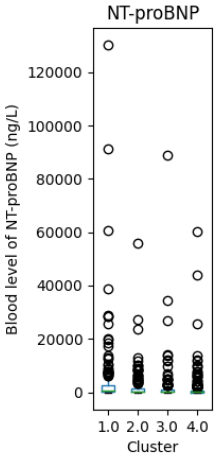

Figure 12: Division of NT-proBNP

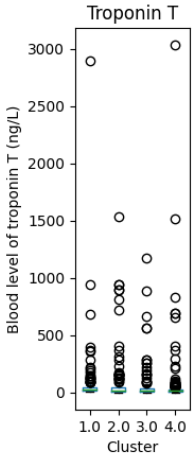

Figure 13: Division of troponin T

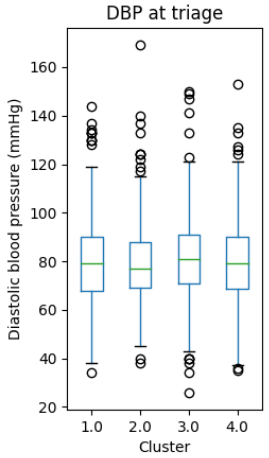

Figure 14: Division of DBP

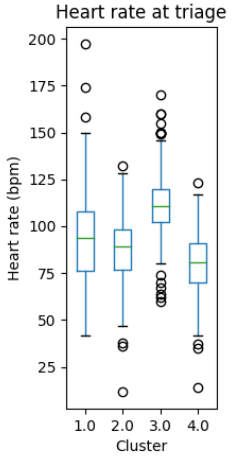

Figure 15: Division of heart rate

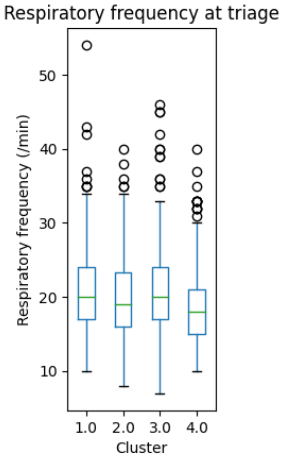

Figure 16: Division of respiratory rate

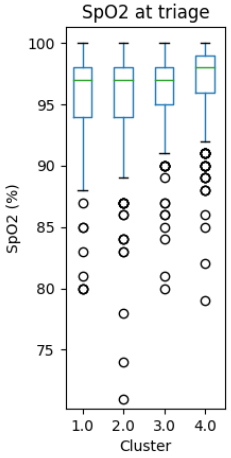

Figure 17: Division of SpO2

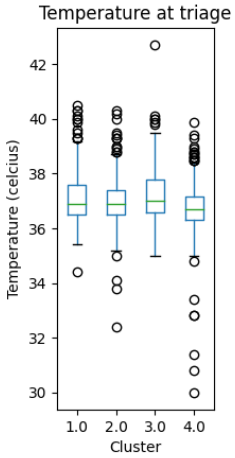

Figure 18: Division of temperature

Appendix C

Table 6: All patient characteristics of the test set divided over the four clusters. P-values equal to or lower than 0.05 are highlighted in bold. *patients who do not smoke are included in the missing values

Characteristic		Missing	Overall	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P-Value
n			100	21	18	16	45	
Biological sex, n (%)	Female	0	50 (50.0)	9 (42.9)	7 (38.9)	8 (50.0)	26 (57.8)	0.492
	Male		50 (50.0)	12 (57.1)	11 (61.1)	8 (50.0)	19 (42.2)	
Age, median [Q1,Q3]		3	66.0 [51.0,74.0]	69.0 [65.0,76.0]	70.0 [51.0,75.0]	50.0 [33.5,61.5]	64.5 [42.5,74.0]	**0.003**
Height, median [Q1,Q3]		80	174.5 [169.8,180.2]	173.0 [170.5,175.5]	181.0 [181.0,181.0]	182.5 [171.2,188.0]	172.0 [167.0,177.0]	0.490
Weight, median [Q1,Q3]		80	82.5 [75.0,87.8]	80.5 [73.0,88.8]	81.0 [81.0,81.0]	87.5 [72.0,94.5]	83.0 [79.0,86.0]	0.958
BMI, median [Q1,Q3]		80	25.5 [24.0,28.2]	24.5 [24.0,28.0]	25.0 [25.0,25.0]	25.0 [23.0,26.8]	27.0 [25.0,28.0]	0.739
Triage colour, n (%)		0					0.708	
	Yellow		66 (66.0)	15 (71.4)	13 (72.2)	8 (50.0)	30 (66.7)	
	Orange		33 (33.0)	6 (28.6)	5 (27.8)	8 (50.0)	14 (31.1)	
	Red		1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	
Transport method, n (%)		0					0.797	
	Self		31 (31.0)	7 (33.3)	4 (22.2)	6 (37.5)	14 (31.1)	
	Ambulance		69 (69.0)	14 (66.7)	14 (77.8)	10 (62.5)	31 (68.9)	
Ambulance urgency, n (%)		0						0.813
	A1	33	10 (14.9)	1 (7.1)	2 (16.7)	1 (10.0)	6 (19.4)	
	A2		54 (80.6)	12 (85.7)	10 (83.3)	9 (90.0)	23 (74.2)	
	B		3 (4.5)	1 (7.1)	0 (0.0)	0 (0.0)	2 (6.5)	
Admission to hospital, n (%)		0	70 (70.0)	19 (90.5)	11 (61.1)	10 (62.5)	30 (66.7)	0.136
Length of stay (h), median [Q1,Q3]		32	94.0 [42.3,183.9]	85.2 [41.4,252.2]	98.5 [76.6,189.8]	50.8 [36.1,155.7]	100.1 [51.5,153.2]	0.775
Mortality, n(%)								
	Within 24 hours	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
	Within 48 hours	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
	Within 72 hours	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
	Within 30 days	0	7 (7.0)	1 (4.8)	2 (11.1)	1 (6.2)	3 (6.7)	0.885
ICU admission, n(%)								
	Within 24 hours	0	2 (2.0)	1 (4.8)	0 (0.0)	1 (6.2)	0 (0.0)	0.311
	Within 48 hours	0	2 (2.0)	1 (4.8)	0 (0.0)	1 (6.2)	0 (0.0)	0.311
	Within 72 hours	0	2 (2.0)	1 (4.8)	0 (0.0)	1 (6.2)	0 (0.0)	0.311
Mortality or ICU admission, n(%)								
	Within 24 hours	0	2 (2.0)	1 (4.8)	0 (0.0)	1 (6.2)	0 (0.0)	0.311
	Within 48 hours	0	2 (2.0)	1 (4.8)	0 (0.0)	1 (6.2)	0 (0.0)	0.311
	Within 72 hours	0	2 (2.0)	1 (4.8)	0 (0.0)	1 (6.2)	0 (0.0)	0.311
Alcohol, n (%)		16	27 (32.1)	0 (0.0)	6 (40.0)	6 (42.9)	15 (40.5)	**0.012**
Smoker, past or present, n (%)		17	39 (47.0)	8 (42.1)	6 (42.9)	8 (61.5)	17 (45.9)	0.706
Last smoke, n (%)		75*						**0.020**
	<2h		2 (8.0)	1 (20.0)	0 (0.0)	1 (20.0)	0 (0.0)	
	<1w		4 (16.0)	0 (0.0)	3 (75.0)	0 (0.0)	1 (9.1)	
	<3m		2 (8.0)	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	
	<1y		2 (8.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (18.2)	
	<10y		2 (8.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (18.2)	
	>10y		13 (52.0)	4 (80.0)	1 (25.0)	2 (40.0)	6 (54.5)	

Characteristic		Missing	Overall	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P-Value
Smoke years, median [Q1,Q3]		70*	30.0 [15.0,43.0]	44.5 [43.0,49.8]	34.0 [15.0,40.0]	25.0 [5.5,37.5]	27.5 [15.2,39.2]	0.147
Pack years, median [Q1,Q3]		0	0.0 [0.0,6.2]	0.0 [0.0,0.0]	0.0 [0.0,6.0]	0.0 [0.0,12.4]	0.0 [0.0,3.8]	0.670
Drugs, n(%)		18	12 (14.6)	1 (5.6)	3 (20.0)	3 (23.1)	5 (13.9)	0.514
Heart rate, median [Q1,Q3]		0	88.0 [76.0,98.2]	91.0 [76.0,102.0]	89.0 [79.2,99.0]	107.5 [98.0,117.8]	82.0 [73.0,89.0]	**<0.001**
SBP, median [Q1,Q3]		1	136.0 [117.0,150.0]	142.0 [123.0,152.0]	136.0 [119.0,138.0]	122.5 [108.2,146.2]	136.0 [114.0,156.0]	0.407
DBP, median [Q1,Q3]		1	79.0 [67.5,87.0]	81.0 [71.0,86.0]	82.0 [75.0,84.0]	78.0 [69.0,85.8]	78.0 [64.0,88.0]	0.847
MAP, median [Q1,Q3]		1	97.0 [85.7,108.2]	98.3 [91.7,109.3]	98.7 [91.3,103.0]	94.3 [83.6,109.4]	96.0 [81.3,114.3]	0.869
Respiratory rate, median [Q1,Q3]		16	19.0 [17.0,23.0]	21.5 [18.0,25.0]	17.0 [16.0,24.0]	18.0 [17.0,22.5]	19.0 [16.0,23.0]	0.353
Temperature, median [Q1,Q3]		12	36.8 [36.5,37.3]	36.8 [36.7,37.6]	36.7 [36.2,37.1]	37.1 [36.7,37.7]	36.8 [36.5,37.1]	0.191
SpO2, median [Q1,Q3]		1	97.0 [95.0,99.0]	97.0 [95.0,99.0]	96.0 [94.0,98.0]	96.5 [94.0,99.2]	98.0 [96.0,99.0]	0.091
Method of oxygen, n(%)		5						0.187
	Room air		71 (74.7)	14 (66.7)	11 (68.8)	10 (66.7)	36 (83.7)	
	Nasal cannula		19 (20.0)	7 (33.3)	3 (18.8)	4 (26.7)	5 (11.6)	
	Non-rebreathing		3 (3.2)	0 (0.0)	2 (12.5)	0 (0.0)	1 (2.3)	
	Larynx mask		2 (2.1)	0 (0.0)	0 (0.0)	1 (6.7)	1 (2.3)	
O2 liters, median [Q1,Q3]		83	3.0 [2.0,4.0]	2.0 [2.0,4.5]	3.0 [2.5,3.5]	3.0 [2.5,3.5]	3.0 [2.8,3.2]	1.000
GCS: total, median [Q1,Q3]		4	15.0 [15.0,15.0]	15.0 [15.0,15.0]	15.0 [15.0,15.0]	15.0 [15.0,15.0]	15.0 [15.0,15.0]	0.707
GCS: Eyes, n(%)		4						0.440
	1		3 (3.1)	0 (0.0)	0 (0.0)	1 (6.7)	2 (4.7)	
	2.0		1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	
	3.0		1 (1.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	
	4.0		91 (94.8)	21 (100.0)	17 (100.0)	13 (86.7)	40 (93.0)	
GCS: Motor, n(%)		4						0.728
	4		2 (2.1)	0 (0.0)	0 (0.0)	1 (6.7)	1 (2.3)	
	5		1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	
	6		93 (96.9)	21 (100.0)	17 (100.0)	14 (93.3)	41 (95.3)	0.728
GCS: Verbal, n(%)		4						0.131
	1		2 (2.1)	0 (0.0)	0 (0.0)	1 (6.7)	1 (2.3)	
	2		2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.7)	
	4		5 (5.2)	2 (9.5)	3 (17.6)	0 (0.0)	0 (0.0)	
	5		87 (90.6)	19 (90.5)	14 (82.4)	14 (93.3)	40 (93.0)	
Blood values, median [Q1,Q3]								
	Sodium	2	138.0 [135.0,140.0]	135.0 [135.0,140.0]	137.5 [132.2,139.0]	138.0 [135.5,140.0]	138.0 [136.0,140.0]	0.525
	Potassium	4	4.0 [3.8,4.4]	4.2 [3.9,4.7]	3.9 [3.6,4.1]	4.0 [3.9,4.2]	4.2 [3.8,4.5]	0.263
	Magnesium	28	0.8 [0.7,0.9]	0.8 [0.7,0.9]	0.8 [0.8,0.9]	0.8 [0.7,0.9]	0.8 [0.7,0.9]	0.823
	Calcium	11	2.3 [2.2,2.4]	2.2 [2.2,2.3]	2.3 [2.2,2.4]	2.4 [2.3,2.4]	2.3 [2.2,2.4]	0.092
	Creatinin	4	83.5 [62.8,121.5]	79 [62.0,122.8]	70.5 [57.2,87.8]	82.0 [70.0,116.0]	91.0 [64.0,125.0]	0.306
	CRP	4	15.0 [3.1,107.5]	39.0 [5.0,122.0]	32.5 [5.4,140.5]	6.0 [2.1,17.5]	12.5 [2.8,84.5]	0.215
	Leukocytes	4	9.1 [6.8,12.4]	9.7 [7.0,11.2]	10.3 [8.2,13.7]	9.8 [7.2,12.6]	8.3 [5.0,12.3]	0.253
	Glucose	6	6.7 [5.8,8.4]	7.8 [6.2,10.2]	6.4 [5.9,7.8]	6.7 [5.5,9.5]	6.6 [5.7,8.1]	0.469
	NT-proBNP	43	392.0 [121.0,1977.0]	363.0 [150.0,1058.5]	373.0 [84.0,1630.0]	255.0 [131.8,816.2]	1142.0 [169.2,3342.8]	0.498
	Troponin T	51	21.0 [9.0,53.0]	38.0 [25.8,56.8]	15.5 [9.0,34.5]	10.5 [5.8,23.0]	27.0 [12.0,58.0]	0.194
	Lactate	15	1.3 [1.0,1.8]	1.1 [0.8,1.3]	1.6 [0.9,2.0]	1.4 [1.1,2.5]	1.4 [1.0,1.7]	0.230
Medication, n(%)								
	Betablockers	0	31 (31.0)	8 (38.1)	5 (27.8)		18 (40.0)	**0.024**
	TCA	0	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.4)	0.476
	Antiarrythmics	0	2 (2.0)	2 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)	0.053
	Digoxin	0	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.4)	0.476
	Diuretics	0	30 (30.0)	7 (33.3)	7 (38.9)	4 (25.0)	12 (26.7)	0.749

Characteristic		Missing	Overall	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P-Value
Charlson comorbidity index, n (%)								
	Myocardial infarction, n (%)	0	8 (8.0)	4 (19.0)	1 (5.6)	0 (0.0)	3 (6.7)	0.163
	Heart failure	0	7 (7.0)	2 (9.5)	2 (11.1)	0 (0.0)	3 (6.7)	0.597
	Peripheral vascular disease	0	5 (5.0)	0 (0.0)	0 (0.0)	1 (6.2)	4 (8.9)	0.316
	CVA or TIA	0	8 (8.0)	1 (4.8)	4 (22.2)	0 (0.0)	3 (6.7)	0.080
	Dementia	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
	Chronic pulmonary disease	0	21 (21.0)	9 (42.9)	3 (16.7)	4 (25.0)	5 (11.1)	**0.029**
	Connective tissue disease		2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.4)	0.476
	Peptic ulcer disease	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
	Mild liver disease	0	3 (3.0)	0 (0.0)	1 (5.6)	0 (0.0)	2 (4.4)	0.600
	Diabetes without complications	0	11 (11.0)	3 (14.3)	3 (16.7)	2 (12.5)	3 (6.7)	0.632
	Diabetes with organ damage	0	4 (4.0)	3 (14.3)	0 (0.0)	0 (0.0)	1 (2.2)	0.056
	Hemiplegia	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
	Severe kidney disease	0	6 (6.0)	3 (14.3)	0 (0.0)	0 (0.0)	3 (6.7)	0.190
	Solid tumor without metastases	0	9 (9.0)	3 (14.3)	0 (0.0)	2 (12.5)	4 (8.9)	0.434
	Leukemia	0	5 (5.0)	3 (14.3)	0 (0.0)	0 (0.0)	2 (4.4)	0.131
	Lymfoma or multiple myeloma	0	6 (6.0)	1 (4.8)	2 (11.1)	0 (0.0)	3 (6.7)	0.583
	Severe liver disease	0	1 (1.0)	0 (0.0)	0 (0.0)	1 (6.2)	0 (0.0)	0.151
	Metastasised solid tumor	0	7 (7.0)	0 (0.0)	1 (5.6)	2 (12.5)	4 (8.9)	0.453
	AIDS	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
CCI: total score, median [Q1,Q3]		0	3.0 [1.0,5.0]	4.0 [3.0,6.0]	3.5 [1.2,5.0]	1.5 [0.0,5.0]	3.0 [1.0,5.0]	0.075
Other comorbidities								
	Pregnancy	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
	Hypertension	0	29 (29.0)	8 (38.1)	7 (38.9)	2 (12.5)	12 (26.7)	0.269
	Hypercholesterolemia	0	9 (9.0)	3 (14.3)	2 (11.1)	0 (0.0)	4 (8.9)	0.494
	PCI or CABG	0	10 (10.0)	4 (19.0)	2 (11.1)	0 (0.0)	4 (8.9)	0.287
	Heart valve replacement	0	4 (4.0)	1 (4.8)	0 (0.0)	0 (0.0)	3 (6.7)	0.516
Organ transplants, n (%)								
	Number of transplants	0						0.821
	0		93 (93.0)	19 (90.5)	18 (100.0)	15 (93.8)	41 (91.1)	
	1		6 (6.0)	2 (9.5)	0 (0.0)	1 (6.2)	3 (6.7)	
	2		1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	
	Kidney	0	5 (5.0)	0 (0.0)	0 (0.0)	1 (6.2)	4 (8.9)	0.316
	Heart	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
	Lung	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
	Liver	0	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	0.745
	Pancreas	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
	Tissue	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
	Stem cell	0	2 (2.0)	2 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)	0.053
Aortic surgeries, n (%)	1	0	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	0.745
Cardiac surgeries		0						0.526
	1		6 (6.0)	3 (14.3)	1 (5.6)	0 (0.0)	2 (4.4)	
	2		3 (3.0)	1 (4.8)	1 (5.6)	0 (0.0)	1 (2.2)	
Aortic and cardiac surgeries, n (%)		0						0.632
	1		7 (7.0)	3 (14.3)	1 (5.6)	0 (0.0)	3 (6.7)	
	2		3 (3.0)	1 (4.8)	1 (5.6)	0 (0.0)	1 (2.2)	

Characteristic		Missing	Overall	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P-Value
Infections, n (%)		0						
	Total		38 (38.0)	10 (47.6)	7 (38.9)	7 (43.8)	14 (31.1)	0.580
	Bacterial		24 (24.0)	5 (23.8)	5 (27.8)	6 (37.5)	8 (17.8)	0.441
	Viral		25 (25.0)	6 (28.6)	5 (27.8)	7 (43.8)	7 (15.6)	0.147
	Fungal or parasitic		2 (2.0)	0 (0.0)	0 (0.0)	2 (12.5)	0 (0.0)	**0.013**
	Central nervous system		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
	Enteritis		18 (18.0)	4 (19.0)	4 (22.2)	5 (31.2)	5 (11.1)	0.310
	Lower respiratory tract		21 (21.0)	5 (23.8)	6 (33.3)	5 (31.2)	5 (11.1)	0.144
	Abdominal		1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	0.745
	Bone or joint		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
	Gastrointestinal		4 (4.0)	2 (9.5)	0 (0.0)	1 (6.2)	1 (2.2)	0.392
	Urinary tract		7 (7.0)	0 (0.0)	1 (5.6)	3 (18.8)	3 (6.7)	0.169
	Skin and soft tissue		2 (2.0)	2 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)	0.053
	Other		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
	Pericarditis		1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	0.745
	Endocarditis		1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	0.745
	Peritonitis		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
	Cholangitis		1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	0.745
	Cholecystitis		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
	Pancreatitis		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Diagnoses, based on IDC-10 codes, n(%)		0						
	Infections (A-B)		11 (11.0)	2 (9.5)	2 (11.1)	3 (18.8)	4 (8.9)	0.745
	Neoplasms (C-D48)		6 (6.0)	2 (9.5)	0 (0.0)	1 (6.2)	3 (6.7)	0.648
	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D5-D8)		10 (10.0)	3 (14.3)	0 (0.0)	2 (12.5)	5 (11.1)	0.457
	Endocrine, nutritional and metabolic diseases (E)		12 (12.0)	4 (19.0)	3 (16.7)	2 (12.5)	3 (6.7)	0.462
	Mental and behavioural disorders (F)		7 (7.0)	1 (4.8)	2 (11.1)	1 (6.2)	3 (6.7)	0.885
	Diseases of the circulatory system (I)		14 (14.0)	3 (14.3)	4 (22.2)	1 (6.2)	6 (13.3)	0.609
	Diseases of the respiratory system (J)		28 (28.0)	7 (33.3)	7 (38.9)	3 (18.8)	11 (24.4)	0.509
	Diseases of the digestive system (K)		7 (7.0)	3 (14.3)	1 (5.6)	1 (6.2)	2 (4.4)	0.525
	Diseases of the skin and subcutaneous tissue (L)		2 (2.0)	2 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)	0.053
	Diseases of the musculoskeletal system and connective tissue (M)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
	Diseases of the genitourinary system (N)		14 (14.0)	4 (19.0)	1 (5.6)	3 (18.8)	6 (13.3)	0.609
	Symptoms, signs and abnormal clinical and laboratory findings not classified elsewhere (R)		37 (37.0)	6 (28.6)	7 (38.9)	6 (37.5)	18 (40.0)	0.839
	Injury, poisoning and certain other consequences of external causes (S-T)		10 (10.0)	1 (4.8)	0 (0.0)	3 (18.8)	6 (13.3)	0.207
	External causes of morbidity and mortality (V-Y)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Department, n(%)		0						
	Acute medicine		34 (34.0)	4 (19.0)	7 (38.9)	5 (31.2)	18 (40.0)	0.382
	Pulmonology		22 (22.0)	6 (28.6)	5 (27.8)	5 (31.2)	6 (13.3)	0.302
	Internal medicine		15 (15.0)	3 (14.3)	2 (11.1)	4 (25.0)	6 (13.3)	0.665
	Gastroenterology		3 (3.0)	1 (4.8)	0 (0.0)	0 (0.0)	2 (4.4)	0.660
	Hematology		12 (12.0)	5 (23.8)	1 (5.6)	0 (0.0)	6 (13.3)	0.125
	Oncology		6 (6.0)	0 (0.0)	1 (5.6)	1 (6.2)	4 (8.9)	0.569
	Nephrology		7 (7.0)	2 (9.5)	1 (5.6)	1 (6.2)	3 (6.7)	0.963
	Reumatology		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
	Urology		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
	Geriatry		1 (1.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0.203

Characteristic		Missing	Overall	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P-Value
Highest SOFA first 24 hours		0						
	0-1		43 (43.0)	7 (33.3)	8 (44.4)	6 (37.5)	22 (48.9)	0.648
	2-5		51 (51.0)	13 (61.9)	10 (55.6)	10 (62.5)	18 (40.0)	0.243
	6-9		6 (6.0)	1 (4.8)	0 (0.0)	0 (0.0)	5 (11.1)	0.230
	10+		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000