Relation of QRS Voltage and Prolonged QTc Interval to One-Year Mortality

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The association between QRS voltage and QTc interval prolongation with mortality for up to 1 year after recording an ECG on patients attending emergency departments (EDs) was examined in a retrospective register-based observational study on 37,473 patients attending 2 Danish EDs. Of 37,473 patients who had an ECG performed on their first ED presentation 2,164 (5.8%) died within 30 days of presentation and 6,395 (17.1%) died within a year. Compared with survivors, patients who died had significantly longer QRS intervals and lower QRS voltages. A combined lead I and II QRS voltage <=1.4 mV was consistently associated with approximately twice the risk of mortality for up to at least 1 year after the ECG recording and this risk was not influenced by the length of the QTc interval. The increased mortality risk of a low QRS voltage remained even after adjustment for age, gender, Charlson co-morbidity index, and abnormal sodium and urea levels. In conclusion, low QRS voltage is a simple measurement that could potentially be used as an objective prognostic marker. **© 2020 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2020;134:138−142)**

There are ECG measurements that nearly all modern machines generate automatically (e.g., heart rate, axis, and PR, QRS, QTc, intervals). QRS voltage amplitude can also be easily and quickly made available at the bedside. QTc prolongation has been associated with all-cause mortality, cardiovascular death, and sudden cardiac death.[1−6] Low QRS voltage has also been associated with an increased risk of mortality. In a study of 6,440 participants free of cardiovascular disease followed up for 13.8 years, the all-cause mortality of patients with low QRS voltage was twice that of those without it: the study defined low QRS voltage as <0.5mV in all frontal leads and/or <1.0 mV in all precordial leads and was observed in only 1.4% of patients.[7] Since QRS amplitude can vary in the leads V1 to V6 because of artifact and errors in chest lead placement, the amplitude of limb ECG Leads I and II, or both combined, have been suggested as the preferred method of measuring QRS voltage.[8,9] Two small pilot studies performed in a low-resource setting in sub-Saharan Africa found an association between the combined QRS amplitudes of Leads I and II with in-hospital mortality.[10,11] This study, with 100% patient follow-up, examined the association between QRS voltage and QTc interval prolongation with mortality for up to 1 year after ECG recordings made on 37,473 patients attending 2 Danish emergency departments (EDs).

Materials and Methods

This study is a retrospective register-based observational cohort study according to STROBE guidelines.[12] The study is based on ED data from March 1, 2013 to April 30, 2014 from 2 Danish hospitals (Odense University Hospital and the Hospital of South West Jutland). In Denmark, the healthcare system is tax-funded, and all residents have free access to healthcare. Odense University Hospital and the Hospital of South West Jutland cover a population of 290,000 and 250,000 people, respectively.

Only the first ECG tracing performed on the first presentation to a participating ED on adults 18 years or older was included in the study. Therefore, there was only one ECG tracing included for each patient. In Denmark, all residents have a unique personal civil registration number, which allows cross-linkage at personal level between databases. We extracted data from several registries: the logistic systems in the ED at the Region of Southern Denmark,[13] the electronic central ECG databases at Region of Southern Denmark, the Danish National Patient Registry,[14] and the Danish Civil Registration System.[15] The previously mentioned databases also provided the patient age, gender, triage status[16] and Charlson Comorbidity Index[17] at the time the ECG tracing was performed, as well as contemporaneous routine laboratory data (i.e., full blood counts, urea, creatinine, electrolytes, and albumin). However, other clinical information such as vital signs, height, and weight, and causes of death were not made available. In the Danish triage system RED and ORANGE indicates the most critical illness.

The QRS amplitude of leads I and II, and QT interval were measured on the first ECG recorded after contact to the ED. All QRS amplitudes and the QT intervals were calculated automatically and stored in the MUSE Cardiology

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One sentence summary: "Patients with a combined lead I and II QRS voltage <=1.4 mV are twice as likely to die within a year."

See page 142 for disclosure information.

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Information System (GE Healthcare). The GE Marquette 12SL ECG Analysis Program provided QRS voltage amplitude and QTc intervals for ECGs recoded in MUSE.[18] The amplitude of lead I and II in all ECGs was measured from the lowest negative deflection (i.e., the Q or S wave) to the highest positive deflection (i.e., the R wave), regardless of the ECG baseline. Only QT intervals corrected for heart rate (QTc) was used in our analysis. For QTc correction, we chose the Framingham Formula (QTcFramingham = QT +0.154 (1−RR))[19]

Our primary outcomes were all-cause mortality within 1, 7, 30, and 365 days after performing the ECG. All patients were followed for 365 days, including those transferred to another department. We compared patient characteristics using Pearson's chi-squared and 2-sample test. Cut-off points for QRS amplitude and QTc was estimated by Youden's method with logistic regressions.[20] Analyses of the 4 mortality outcomes were conducted as Cox proportional hazards modelling. Analyses was conducted as raw and adjusted analyses that included potentially confounding covariants (i.e., age, gender, triage category, co-morbidity, haemoglobin level, white cell and platelet count, sodium, potassium, urea, creatinine, and albumin level). The assumption of proportional hazards was investigated by Schoenfeldt residuals. Kaplan−Meier survival curves were compared by the log-rank test. Graphic survival analysis was performed using the Online Application for the Survival Analysis software available at http://sbi.postech.ac.kr/oasis/surv/.[21] All other statistical analyses were performed using Stata 15 (Stata Corp LP, College Station, Texas), and a significance level of 5 % was applied.

This study complies with the Declaration of Helsinki. It was without contact to patients and according to Danish law it did not require approval from Ethics Committees. The study was approved by the Danish Data Protection Agency (file no. 2008-58-0035, project ID 20-1248) and the Danish Health and Medicines authority (file no. 3-3013-1031).

Results

During the study period 37,473 patients had an ECG performed on their first ED presentation: 2,164 (5.8%) died within 30 days of presentation and 6,395 (17.1%) died within a year. Compared with survivors, patients who died within a year were significantly older (76.2 standard deviation [SD] 12.4 vs 61.2 SD 18.9 years, p <0.0001) and had lower lead I and II voltage (1.6 SD 0.8 vs 1.8 SD 0.6 mV, p <0.0001) and longer QTc intervals (426 SD 36 vs 423 SD 31 ms, p <0.0001). Lead I+II voltage ranged from 1.3 to 2.1 mV and 365-day mortality increased exponentially from 16.4% to 39.1% as voltage decreased (Supplemental Figure A)

QRS voltage and QTc intervals were converted to categorical variables using the Youden statistic (Table 1). Overall, the optimal Lead I+II cut-off for all patients ranged from 1.3 at day 1 to 1.5 mV at 365 days, and there was no significant difference between men and women. The optimal cut-off for QTc interval varied by age and gender and ranged from 435 ms at 7 days to 433 ms at 365 days. Based on these findings the following cut-offs were arbitrarily adopted to simplify further analysis: 1.4 mV for Lead I+II, and 434 ms for QTc interval. Using these cut-offs more than a quarter of all patients had a low QRS voltage or a prolonged QTc interval. Patients with a low QRS voltage were more likely to die than those with a prolonged QTc interval and were more than twice as likely to die at any time up to 1 year. Male patients were more likely to have low QRS voltage and prolonged QTc interval than female patients. More ECG's were performed on older patients, and there was an equal linear increase in proportion of patients with low QRS voltage and a prolonged QTc interval with age (Supplemental Figure B). Also, patients with a low QRS voltage and/or prolonged QTc interval had higher triage codes, a higher co-morbidity index, and were more likely to have laboratory abnormalities (Table 2).

Table 1.
Optimal cut-offs calculated by the Youden statistic for the association of Lead I+II voltage and QTc interval with mortality at different time intervals, and according to age and gender

	Mortality at:			
	1 day	7 days	30 days	365 days
Lead I+II voltage (mV)				
Age <64 years	1.4	1.6	1.5	1.5
Age >=64 years	1.4	1.4	1.4	1.5
Men	1.4	1.4	1.5	1.5
Women	1.3	1.4	1.4	1.4
All patients	1.4	1.4	1.4	1.5
QTc interval (ms)				
Age <64 years	434	435	441	436
Age >=64 years	443	393	395	405
Men	434	435	433	433
Women	438	443	395	404
All patients	434	435	434	433

ms = milliseconds; mV = millivolts.

Age, gender, Charlson co-morbidity index, abnormal sodium and urea levels were the only variables that met the assumption of proportional hazards in a Cox model and were, therefore, used to determine adjusted hazards ratios. At all the time intervals after ECG recording Lead I+II voltage had the highest unadjusted and adjusted hazards ratios, and after adjustment a prolonged QTc interval only had a significant hazards ratio for increased mortality at 7 days, and a slight but significant reduced hazard ratio for mortality at 365 days (Table 3).

QTc prolongation did not influence the relationship between QRS voltage and mortality. As demonstrated by the hazard ratio for mortality for the 4 possible combinations of normal and abnormal QRS voltage and QTc interval (Table 4). The Kaplan-Meier survival curves of patients with a low Lead I+II voltage with or without QT prolongation were identical, and significantly different from the survival curves of those with Lead I+II voltages >1.4 mV with or without normal QTc intervals. (Figure 1).

Discussion

A combined lead I and II QRS voltage <=1.4 mV was consistently associated with approximately twice the risk of mortality for up to at least 1 year after the ECG was

Table 2.
Continuous and categorial variables associated with QRS voltage and QTc prolongation

V Variable	Total(n = 37,473)	Lead I+II			QTc		
		>1.4 mV (n = 26,713)	<=1.4 mV (n = 10,760)	p-value	<434 (n = 26,673)	>=434 (n = 10,800)	p-value
Age at ECG tracing	63.9 (SD 18.9)	61.2 (SD 19.6)	70.2 (SD 15.3)	<0.001	61.2 (SD 19.5)	69.9 (SD 16.0)	<0.001
Male gender	18,767 (50.1%)	12,991 (48.9%)	5,776 (53.0%)	<0.001	13,277 (50.8%)	5,490 (48.4%)	<0.001
Triage class							
Red	1,462 (4.2%)	956 (3.9%)	506 (4.9%)	<0.001	977 (4.0%)	485 (4.6%)	0.092
Orange	7,109 (20.3%)	5,005 (20.2%)	2,104 (20.6%)		4,997 (20.4%)	2,112 (20.0%)	
Yellow	14,544 (41.5%)	10,130 (40.9%)	4,414 (43.2%)		10,178 (41.6%)	4,366 (41.4%)	
Green	11,368 (32.5%)	8,325 (33.6%)	3,043 (29.8%)		7,929 (32.4%)	3,439 (32.6%)	
Blue	522 (1.5%)	365 (1.5%)	157 (1.5%)		374 (1.5%)	148 (1.4%)	
Charlson Index							
0	15,981 (42.6%)	12,757 (48.0%)	3,224 (29.6%)	<0.001	12,038 (46.1%)	3,943 (34.8%)	<0.001
1−2	13,231 (35.3%)	8,906 (33.5%)	4,325 (39.7%)		9,085 (34.8%)	4,146 (36.6%)	
>2	8,261 (22.0%)	4,909 (18.5%)	3,352 (30.7%)		5,016 (19.2%)	3,245 (28.6%)	
Mortality							
Day 1	344 (0.9%)	166 (0.6%)	178 (1.7%)	<0.001	195 (0.7%)	149 (1.4%)	<0.001
Day 7	973 (2.6%)	490 (1.8%)	483 (4.5%)	<0.001	613 (2.3%)	360 (3.3%)	<0.001
Day 30	2164 (5.8%)	1129 (4.2%)	1035 (9.6%)	<0.001	1388 (5.2%)	776 (7.2%)	<0.001
Day 365	6395 (17.1%)	3621 (13.6%)	2774 (27.8%)	<0.001	4146 (15.5%)	2249 (20.8%)	<0.001
QTc interval (ms)	422.6 (SD 30.8)	422.2 (SD 29.2)	423.5 (SD 34.2)	<0.001	407.6 (SD 18.1)	457.2 (SD 25.8)	<0.001
Lead I amplitude (mV)	0.86 (SD 0.39)	0.98 (SD 0.39)	0.56 (SD 0.20)	<0.001	0.86 (SD 0.37)	0.86 (SD 0.45)	0.84
Lead 2 amplitude (mV)	0.87 (SD 0.43)	0.99 (SD 0.43)	0.56 (SD 0.20)	<0.001	0.86 (SD 0.38)	0.87 (SD 0.52)	0.12
Lead I+II amplitude (mV)	1.73 (SD 0.62)	1.98 (SD 0.56)	1.12 (SD 0.22)	<0.001	1.73 (SD 0.54)	1.73 (SD 0.79)	0.35
Haemoglobin (g/dl)	12.96 (SD 2.09)	13.12 (SD 2.03)	12.58 (SD 2.19)	<0.001	13.10 (SD 2.06)	12.63 (SD 2.13)	<0.001
White blood count (10^9/L)	10.10 (SD 6.21)	9.91 (SD 5.86)	10.55 (SD 6.96)	<0.001	10.27 (SD 6.40)	9.73 (SD 5.75)	<0.001
Platelet count (10^9/L)	253.6 (SD 98.6)	253.5 (SD 95.8)	253.7 (SD 105.0)	0.87	257.7 (SD 99.3)	244.1 (SD 96.3)	<0.001
Sodium (mmol/L)	137.4 (SD 4.9)	137.6 (SD 4.7)	136.8 (SD 5.2)	<0.001	137.4 (SD 4.7)	137.4 (SD 5.2)	0.79
Potassium (mmol/L)	3.9 (SD 0.6)	3.8 (SD 0.5)	4.0 (SD 0.6)	<0.001	3.9 (SD 0.5)	3.8 (SD 0.6)	<0.001
Urea (mmol/L)	7.5 (SD 6.1)	7.1 (SD 5.5)	8.6 (SD 7.3)	<0.001	7.2 (SD 5.7)	8.4 (SD 6.9)	<0.001
Creatinine (mmol/L)	98.7 (SD 77.0)	95.0 (SD 69.6)	107.66 (SD 91.7)	<0.001	94.7 (SD 71.3)	108.1 (SD 88.0)	<0.001
Albumin (mg/L)	38.5 (SD 5.0)	39.2 (SD 4.7)	36.7 (SD 5.4)	<0.001	38.8 (SD 5.0)	37.8 (SD 5.0)	<0.001

Data are presented as mean (SD) for continuous measures, and n (%) for categorical measures.

Table 3
Unadjusted and adjusted hazard ratios for mortality associated with QRS voltage and QTc prolongation

	Number (%)	Day	Mort%	Unadjusted			Adjusted*		
				Hazard ratio	(95% CI)	p	Hazard ratio	(95% CI)	p
Lead I+II <=1.4 mV	10760 (28.7%)	1	1.7%	2.31	(1.76 3.03)	<0.0001	1.71	(1.29 2.26)	<0.0001
		7	4.5%	2.34	(2.04 2.68)	<0.0001	1.58	(1.37 1.82)	<0.0001
		30	9.6%	2.28	(2.09 2.49)	<0.0001	1.48	(1.35 1.62)	<0.0001
		365	25.8%	2.04	(1.94 2.14)	<0.0001	1.32	(1.26 1.39)	<0.0001
QTc >=434 ms	10800 (28.8%)	1	1.4%	1.98	(1.51 2.60)	<0.0001	1.47	(1.11 1.95)	0.01
		7	3.3%	1.41	(1.23 1.62)	<0.0001	0.99	(0.86 1.14)	0.90
		30	7.2%	1.37	(1.25 1.50)	<0.0001	0.94	(0.86 1.03)	0.21
		365	20.8%	1.36	(1.30 1.44)	<0.0001	0.93	(0.88 0.98)	0.01

ms = milliseconds; mV = millivolts.
* Adjusted for age, gender, Charlson index, sodium, and urea levels within the normal ranges.

recorded and this risk was not influenced by the length of the QTc interval. The mortality risk of low QRS voltage remained even after adjustment for age, gender, Charlson co-morbidity index, and abnormal sodium and urea levels, the only variables identified by Cox regression that consistently influenced mortality over time. Any influence that the other variables tested had over mortality was either non-existent or transient.

The strengths of this study were that it was large, examined data from 2 Danish EDs and provided 100% follow-up of all patients in and out of hospital so that there were no unrecorded deaths.[13−15] Nevertheless, this register-based and retrospective study had several limitations. Vital signs, height, weight, and causes of death were not made available and could not be tested. The ECG measures were all automatic readouts, and we did not manually validate QRS amplitude or the QTc interval length. However, the automatic ECG measurement method used had been previously validated,[5] but only for QTc interval measurement. We arbitrarily selected one QTc interval as a comparator and

Table 4
Hazards ratio for mortality for patients for the four possible combinations of normal and abnormal QRS voltage and QTc interval

Day of death	Lead I+II <1.4 mV	QTc >434 ms	Patient number	Unadjusted			p-value	Adjusted			p-value
				Hazard ratio	95% CI			Hazard ratio	95% CI		
1	No	No	19,330	1.00				1.00			
	No	Yes	7,413	3.27	2.23	4.78	<0.0001	2.29	1.55	3.40	<0.0001
	Yes	No	7,373	3.75	2.58	5.46	<0.0001	2.58	1.76	3.79	<0.0001
	Yes	Yes	3,387	4.04	2.60	6.27	<0.0001	2.46	1.56	3.86	<0.0001
7	No	No	19,330	1.00				1.00			
	No	Yes	7,413	2.18	1.68	2.84	<0.0001	1.46	1.11	1.91	0.01
	Yes	No	7,373	3.27	2.57	4.16	<0.0001	2.10	1.64	2.70	<0.0001
	Yes	Yes	3,387	3.39	2.54	4.53	<0.0001	1.84	1.37	2.48	<0.0001
30	No	No	19,330	1.00				1.00			
	No	Yes	7,413	1.94	1.60	2.35	<0.0001	1.27	1.04	1.54	0.02
	Yes	No	7,373	3.06	2.58	3.64	<0.0001	1.90	1.59	2.27	<0.0001
	Yes	Yes	3,387	2.82	2.27	3.50	<0.0001	1.47	1.18	1.84	<0.0001
365	No	No	19,330	1.00				1.00			
	No	Yes	7,413	1.58	1.48	1.69	<0.0001	1.02	0.95	1.09	0.67
	Yes	No	7,373	2.33	2.19	2.48	<0.0001	1.41	1.33	1.51	<0.0001
	Yes	Yes	3,387	2.46	2.27	2.65	<0.0001	1.19	1.10	1.29	<0.0001

ms = milliseconds; mV = millivolts.

did not exclude ECGs of patients with conditions that might influence QTc measuring, such as atrial fibrillation. In addition, it was not possible to identify if patients were taking drugs and/or other factors that might have influenced ECG findings.

In addition to cardiac and pericardial disease low QRS voltage has also been observed in many non-cardiac conditions such as pleural effusions, emphysema, pulmonary infiltrations, and hypothyroidism[22] and reported to be more common in the elderly, in women, non-Hispanic blacks and those with pulmonary disease, and malignancies.[7] This study confirms previous reports that patients with low QRS voltage are more likely to die than those without it.[7,10,11] The mechanisms that determine QRS amplitude are unclear. Madias has written extensively on the topic and believes that it is greatly influenced by water content of the organs and tissues surrounding heart.[23] This may explain why low QRS voltage has been reported in patients with peripheral oedema from any cause, including perioperative fluid load administration, chronic renal failure, congestive heart failure, and hepatic cirrhosis.

This study found that more than a quarter of ED patients have a Lead I+II QRS voltage <=1.4 mV, which is associated with an increased risk of death. Although the risk

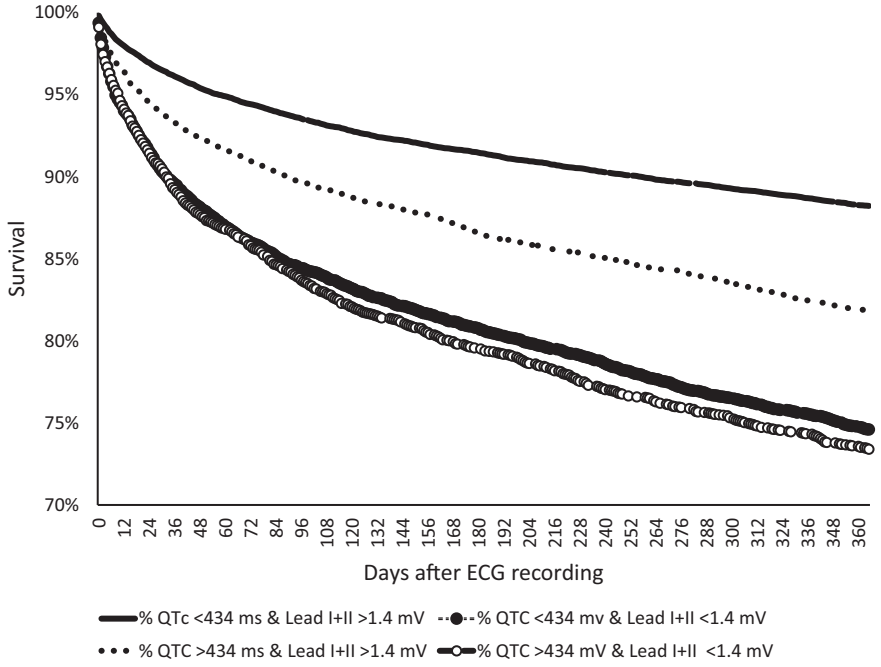

Figure 1. 365-day Kaplan-Meier survival curves of patients with normal QRS voltage and normal QTc interval (First curve on top), normal QRS voltage and prolonged QTc interval (Second curve), low QRS voltage and normal QTC interval (Third curve), and low QRS voltage and prolonged QTc interval. All curves were statistically different from each other (p <0.0001), except for third and fourth curves, which were statistically the same (p = 0.57).

tended to be highest immediately after the ECG was recorded, it only reduced slightly over the next 365 days. It is, therefore, not clear if QRS voltage changes are best suited to short or to long term predictions. Unlike the QTc interval, this categorical measurement was little influenced by the patient's age or gender and the time elapsed after ECG recording. The measurement is easy to make as it requires no calculation, little training or skill, and incurs no additional costs. Many factors are associated with imminent death such as triage status, acute ischaemia and electrolyte abnormalities, and might transiently influence the ECG tracing, whereas factors such as age, gender, and co-morbidity are persistently associated with an increased the risk of death. Even when adjusted for these variables, patients with a low QRS voltage, unlike those with QTc prolongation, were significantly more likely to die at any time up to at least a year after the ECG being recorded. In conclusion, low QRS voltage is a simple measurement that could potentially be used as an objective prognostic marker and requires little skill or expense to obtain.

Ethics Declaration

This study complies with the Declaration of Helsinki and was without contact to patients. According to Danish law this study did not require approval from Ethics Committees.

Data Availability Statement

Data of this study are available to all interested parties upon request, pending approval from the Danish Data Protection Agency.

Disclosures

John Kellett is a major shareholder, director and chief medical officer of Tapa Healthcare DAC. The other authors have no potential conflict of interest.

Authors Contributions

All authors contributed to the preparation of this study. SBB, JK and MB conceived the study; MB and UE supervised the collection of the data and ensured its accuracy, SBB and JK analyzed the data; SBB, JK and MB drafted the manuscript and critically revised the manuscript for intellectual content. All authors read and approved the final manuscript and are guarantors of the study.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.08.008.

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