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Prognostic Value and Limits of Heart Rate and QT—Corrected in A Large Population

Paolo Giovanardi [1,2,*], Cecilia Vernia [3], Sara Roversi [4], Enrico Tincani [5], Giuseppe Spadafora [1], Federico Silipo [6] and Claudio Giberti [7]

1 Cardiology Service, Department of Primary Care, Health Authority and Services of Modena, Via del Pozzo 71, 41125 Modena, Italy; g.spadafora@ausl.mo.it
2 Cardiology Unit, Ospedale S.Agostino–Estense, Department of Nephrological, Cardiac and Vascular Diseases, Azienda Ospedaliero-Universitaria Modena, Via Giardini 1355, 41126 Baggiovara, Italy
3 Department of Physics, Informatics and Mathematics, University of Modena and Reggio Emilia, Via G. Campi 213/b, 41125 Modena, Italy; cecilia.vernia@unimore.it
4 Primary Care, Department of Primary Care, Health Authority and Services of Modena, Via Giardini 476, 41126 Modena, Italy; rov_sara@yahoo.it
5 Internal Medicine Division, Department of Internal Medicine, Ospedale S.Agostino–Estense, Azienda Ospedaliero-Universitaria Modena, Via Giardini 1355, 41126 Baggiovara, Italy; e.tincani@gmail.com
6 Department of Clinical Engineering, Health Authority and Services and Azienda Ospedaliero-Universitaria Modena, Via del Pozzo 71, 41125 Modena, Italy; f.silipo@ausl.mo.it
7 Department of Sciences and Methods for Engineering, University of Modena and Reggio Emilia, Via Amendola 2, 42122 Reggio Emilia, Italy; claudio.giberti@unimore.it
* Correspondence: p.giovanardi@ausl.mo.it or p.giovanardi@mail.com; Tel.: +39-059438741

Abstract: Background: The study aimed to compare the prognostic importance of the heart rate (HR) and QT—corrected (QTc) according to Fridericia, Framingham, and Bazett with respect to all-cause mortality in a large non-selected population. Methods: The analysis of digital electrocardiograms archived from 2008 to 2022 in the metropolitan area of Modena, Italy, was carried out. The population under study was divided into three groups based on age, and survival analysis was performed. Results: 131,627 patients were enrolled and, during the follow-up (mean 1641.4 days), all-cause mortality was 8.9%. Both HR and QTc were associated with mortality. All-cause mortality significantly increased with HR values greater than 81 BPM and QTc values greater than 440 msec in young subjects and 455 msec in old subjects (values of the 75th percentiles/optimal operating point). A Cox analysis confirmed the better prognostic value of Bazett's QTc and HR in the whole population and in the three age-groups. Conclusion: Bazett's method performed better than the others, but, unexpectedly, the HR had the same or an even better correlation with all-cause mortality. Since the HR is simple and readily available, its evaluation should be improved. However, QTC and HR values are difficult to define, causing many confounding factors, and further population studies are required.

Keywords: electrocardiogram; QT—corrected; Bazett; heart rate; all-cause death; mortality

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1. Introduction

The closely related QT interval and heart rate (HR) are considered, even with some controversial evidence, to be predictors of death [1,2].

The QT interval on the surface electrocardiogram (ECG) represents the time from the onset of ventricular depolarization to the end of repolarization and is mediated by ion channels, which are molecular structures in the membranes of myocardial cells. Both QT shortening and QT prolongation correlate with a poor prognosis, being associated with potentially fatal arrhythmias such as torsade de pointes, ventricular tachyarrhythmias, and sudden cardiac death [3]. QT prolongation has two main aetiologies: congenital (i.e., inherited long-QT syndrome) [4] and acquired. Different factors have been related to the acquired long-QT, including demographic risk factors, pollution, drugs, cardiovascular

risk factors, electrolyte disorders, stroke, altered autonomic tone, and structural heart diseases [5–9]. The QT interval, according to HR, changes: it increases at a low HR and decreases at a high HR. To normalize such variability, many methods have been devised and are currently available in clinical practice, to correct the QT interval according to the HR (QTc) [10,11].

Conversely, the HR is a simple, inexpensive, and easily measurable biological parameter. Similarly to the QT interval, the HR is also influenced by many conditions such as genetics, cardiovascular risk factors and cardiovascular diseases, infections, inflammatory diseases, drug use, physical activity, and sympathetic and vagal imbalance [12–15]. Furthermore, the HR has been described as a relevant predictor of all-cause and cardiovascular mortality, despite the fact that it is often overlooked [2].

This study aimed to assess the risk of all-cause mortality through the evaluation of the HR and QTc, calculated utilizing the Bazett, Fridericia, and Framingham methods, in a large, non-selected, primary, adult, European population subdivided into age-groups.

2. Material and Methods

The study was performed according to the Ethical Standards of the 1975 Helsinki Declaration revised in 2013 and was approved by the local Ethic Committee of Modena (AVEN), protocol number 2605/2021, date of approval 21 September 2021. Due to the anonymous and observational nature of the study, informed consent could not be obtained from the enrolled patients.

2.1. Study Population

The metropolitan area of Modena, located in south-central Emilia-Romagna, Italy, has a population of 702,635 people (www.provincia.modena.it, last accessed on 1 October 2022) spread across 47 municipalities. National Health general practitioners refer their patients to the National Health System core facilities for clinical tests. ECGs are recorded in the emergency departments, in hospitals (surgical and medical units, day-hospital, day-services, and pre-operative screening), and in- and out-of-hospital patient clinics.

Patients with a digitized ECG archived in any facility in the metropolitan area of Modena from January 2008 to October 2022 were eligible.

Cardiovascular risk factors in the resident population included: diabetes (a metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion or action), systemic arterial hypertension (the increase in systolic and or diastolic blood pressure above 140/90 mmHg), dyslipidemia (the disorders in lipoprotein metabolism causing an increase in the blood levels of cholesterol and/or triglycerides), and tobacco smoke (the active exposure to tobacco products).

The main cardiovascular diseases in the resident population included: heart failure (the syndrome with symptoms and or signs caused by structural and/or functional cardiac abnormalities), coronary artery diseases (the group of diseases characterized by the reduction in blood flow into the heart muscle causing the partial or complete blockage of the coronary flow), and stroke (a neurological deficit due to a cerebrovascular cause).

The main comorbidities in the resident population included: chronic obstructive pulmonary disease (the chronic inflammatory lung disease that obstructs the airflow), dementia (the chronic deterioration of cognitive function not expected from the consequences of biological ageing), cancer (the large group of diseases starting from abnormal cells growing uncontrollably in any tissue of the body that can potentially invade other organs), and chronic kidney disease (a kidney damage or glomerular filtration rate that stays lower than 60 mL/min/1.73 m^2 for more than three months).

The prevalence of CV risk factors in the resident population was: diabetes at 5.7%; systemic arterial hypertension at 23.1%; dyslipidemia at 38.8%; and tobacco smoke at 17.1%. Among CV diseases and comorbidities: CV diseases at 7.9%; cerebrovascular diseases at 1.5%; chronic obstructive pulmonary diseases at 7.5%; dementia at 3.1%; cancer at 5.1%; and chronic kidney disease at 1.2%.

Age and sex were also anonymously collected.

2.2. Electrocardiography

ECGs were recorded at rest, usually in a quite environment, in the supine position using a standard 12-lead tracing at 25 mm/s speed, and 10 mm/mV amplitude, with a sampling rate of at least 500 Hz, and were archived in a "MUSE®" electronic archive (GE Marquette Medical System, Milwaukee, WI, USA). Automated analyses were performed through a digitized multi-channel computer-assisted program (GE 12SL ECG Analysis), a healthcare system that uses validated algorithms. ECG diagnoses were supervised and confirmed by trained cardiologists.

ECGs were discarded when they turned out to be incomplete or when they had technical problems such as a bad signal quality (causing failure in the evaluation of ECG parameters), waveform recognition errors, and electrode interchanges, or in the presence of a pacemaker or implantable cardioverter-defibrillator. ECGs were also discarded in patients suffering from atrial fibrillation or atrial flutter, supraventricular or ventricular tachycardia, Wollf–Parkinson–White syndrome, second- or third-degree A-V block, with complete or incomplete left or right bundle-branch block, with a QRS duration greater than 140 msec, with a QTc duration greater than 650 msec or lower than 280 msec due to artifacts, and in the presence of more than three premature beats.

In the case of patients with multiple ECGs archived in the dataset, only the first was used for the present study with the aim to include ECGs at first medical contact and to reduce the influence of drugs.

HR was automatically calculated from the stored ECGs, and QTc was digitally measured utilizing Bazett, Fridericia, and Framingham correction from the mean of the QT interval of the 12 ECG leads.

The quality control on the ECGs consisted of two steps: the first was provided by the GE healthcare analysis system and the second by the validation made by clinicians.

2.3. Other Inclusion/Exclusion Criteria

Young patients (up to 25 years of age) and very old people (more than 85 years of age) were excluded. Since the whole population was not homogeneous, the enrolled patients were also divided into three age-groups: group 1 was composed of subjects between 25 and 45 years of age, group 2 was composed of subjects between the ages of 46 and 65, and group 3 consisted of subjects aged 66 to 85.

2.4. Follow-Up

All-cause mortality and emigrations were retrospectively evaluated through an anonymous numeric personal identification code utilizing electronic medical records of the Health Authority and Services of the Province of Modena.

All emigrated people were excluded from the follow-up.

2.5. Statistical Analysis

Continuous variables are displayed as mean ± standard deviation, while categorical data are displayed as frequencies.

T-test was used to compare means for clinical and ECG data to check the null hypothesis that the average of two subpopulations were different. The three mean values of the different QTc formulae were compared using one-way ANOVA analysis, followed by pairwise t-test comparisons with Holm–Bonferroni correction. Linear regression was used to test the independence of the QTc values from HR using R wave to R wave interval (RR interval = 60/HR in milliseconds).

To establish the optimal operating point, the receiver operating characteristic (ROC) curves for QTc methods and for HR were constructed.

The survival analysis was performed for the end point of all-cause mortality at follow-up. Rates of mortality were computed for the individuals whose QTc and HR values

were, respectively, below the 25th percentile and above the 75th percentile in the whole population and in the three age-groups. Cumulative endpoint event rates were analyzed through the Kaplan–Meier event-free survival method.

In the whole population, according to the three age-groups and stratifying for sex, a forward Cox proportional hazard model was used to estimate the relative risk, denoted Exp B, and to assess the performance of a multivariable model for HR and for the three considered QTc methods.

All the statistical tests with a p-value < 0.05 were considered significant and the confidence intervals were taken at level 95%. In the case of multiple testing, the Holm–Bonferroni method was applied to verify the statistical significance of our data.

3. Results

From January 2008 to October 2022, in the National Health System facilities of Modena, 375,207 ECGs were archived in the GE Marquette Healthcare Analysis Program. From these ECGs, after exclusions, 131,627 subjects were enrolled.

Table 1 shows the baseline clinical and ECG characteristics of the enrolled patients and exclusion criteria. Females had longer QTc values and higher HR values compared to males (while males had an older mean age and higher rates of mortality compared to females). In the entire population and the three facilities, Bazett's QTc values were longer than those obtained with other correction methods.

Table 1. Clinical and ECG baseline characteristics of the study population and exclusion criteria.

Clinical Characteristics of the Enrolled Population		**QTc and Heart Rate in the Three Facilities**	
Enrolled Patients	131,627	**Emergency Department Group**	29,010
Men 64,386 (48.9%)	Women 67,241 (51.1%)	QTc Bazett °	435.8 ± 28.2 *
Mean enrollment age (years) *	57.5 ± 16	QTc Fridericia °	423.1 ± 26.6 *
Men * 58.3 ± 15.3	Women * 56.8 ± 16.6	QTc Framingham °	420.4 ± 24.5 *
Number of deaths in the follow-up period	11,727 (8.9%)	HR	76.6 ± 16.4 *
Men 6370 (54.3%)	Women 5357 (45.7%)	**Surgical/Medical Units Group**	85,604
Mean Heart Rate *	72.6 ± 14.3	QTc Bazett °	429.6 ± 28.4 *
Men * 70.8 ± 14.4	Women * 74.3 ± 13	QTc Fridericia °	420.7 ± 25.9 *
		QTc Framingham °	418.6 ± 24 *
ECG Characteristics of the Enrolled Population		HR	71.9 ± 13.6 *
QRS duration °	89.3 ± 13	**Ambulatory Group**	17,013
T duration °	189.7 ± 39.6	QTc Bazett °	421.6 ± 23.3 *
QTc Bazett °	429.1 ± 28.1	QTc Fridericia °	413.3 ± 19.6 *
QTc Fridericia °	420.2 ± 25.5	QTc Framingham °	413.9 ± 19.2 *
QTc Framingham °	418.4 ± 23.6	HR	69.0 ± 11.7 *
Exclusion Criteria (243,580 ECGs)			
Incorrect and bad signal qualities ECG	14,087	Atrial tachycardias and tachiarrythmias	21358
Young and very old people	46,378	Bundle branch block	25145
Multiple ECG	118,595	Second- and third-degree AV block	1768
Pacemaker, implantable defibrillator	4748	Others	11,501

% percentage of patients, * mean ± standard deviation, ° milliseconds.

A one-way ANOVA analysis performed for the QTc mean values indicates that their differences are statistically significant. In Table 2 (upper panel), the results of the pairwise

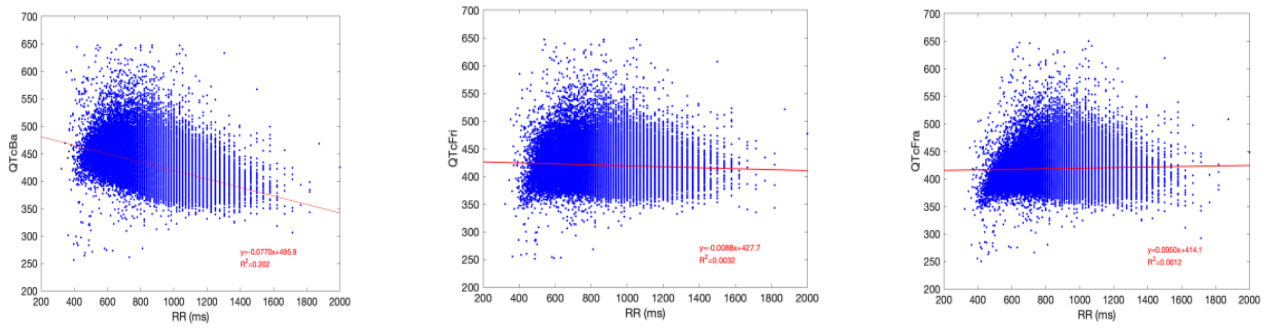
t-test comparison for the three QTc methods show that Bazett's correction is significantly longer than the other methods.

Table 2. Results of the pairwise t-test comparison of the QTc values (upper panel) and linear regressions between QTc and RR interval (lower panel).

Comparison	Mean Difference (msec)	95% CI °	*p*
QTc Bazett vs. QTc Fridericia	9.71	[9.66, 9.78]	<0.001
QTc Bazett vs. QTc Framingham	11.54	[11.46, 11.62]	<0.001
QTc Fridericia vs. QTc Framingham	1.825	[1.78, 1.87]	<0.001
Linear Regression QTc vs. RR * Interval			
	Slope	**95% CI °**	**R^2 ^**
QTc Bazett	−0.077	[−0.078, −0.076]	0.198
QTc Fridericia	−0.086	[−0.094, −0.008]	0.003
QTc Framingham	0.0052	[0.004, 0.006]	0.001

° confidence interval, * R wave to R wave interval, ^ goodness of fit.

The linear regressions of each QTc method vs. RR interval are represented in Figure 1, while the slopes of the linear fits together with their 95% confidence intervals are reported in the lower panel of Table 2. These results show that Framingham's correction has greater independence from RR with respect to the other methods, as evidenced by the R^2 and slope values closest to zero.



(**a**) (**b**) (**c**)

Figure 1. Linear regression between QTc and RR for Bazett (**a**), Fridericia (**b**), and Framingham (**c**) QTc.

During the follow-up period (mean follow-up of 1641.4 days), 11,727 subjects (8.9%) had died of all-cause mortality (6370 men and 5357 women, see Table 1). Table 3 shows the rates of mortality for the three QTc methods and the HR according to the 25th and the 75th percentile. In the whole population, the increase in the relative risk of mortality (Exp B) for the QTc methods and the HR was statistically significant over the 75th percentile, with Bazett's correction performing better. Instead, in each of the three age-groups, the relative risk of mortality (Exp B) over the 75th percentile was significantly greater for the HR and Bazett's method. Due to the heterogeneity of the enrolled population, mortality rates according to the 25th and the 75th percentile have also been calculated in each of the three facilities (emergency departments, hospital units, and in- and out-of-hospital patient clinics) observing in each of them similar behaviours with respect to the entire population. In ambulatory patients, the smallest group with lower mortality rates, the QTc had a lower significance (see Table S1 in Supplemental Materials).

ROC curves for each of the three QTc methods and for the HR were constructed in the whole population and in the three age-groups, revealing areas under the curve (AUCs)

from 0.665 to 0.567. Optimal operating points were superimposable to the 75th percentile (see Figure S1 in Supplemental Materials).

Table 3. Rates of mortality for the three QTc methods and for HR according to 25th and 75th percentile in the whole population and in the three age-groups. Relative risk reveals the increased risk of all-cause mortality in subjects with a QTc and an HR above the 75th percentile.

Whole Population: 131,627 Patients									
	Median	**25th Percentile**	**75th Percentile**	**25th Percentile Mortality (%)**	**75th Percentile Mortality (%)**	**B**	***p***	**Exp (B) ***	**95% CI ^**
QTc Bazett °	428	412	446	9.55	20.3	0.927	<0.001	2.527	[2.447, 2.61]
QTc Fridericia °	418	404	434	7.14	9.5	0.798	<0.001	2.221	[2.15, 2.294]
QTc Framingham °	416	404	431	7.6	9.46	0.788	<0.001	2.198	[2.128, 2.271]
HR	71	63	81	8.65	16.72	0.607	<0.001	1.835	[1.775, 1.897]
Group 1 (25–45 Years): 33,849 Patients									
	Median	**25th Percentile**	**75th Percentile**	**25th Percentile Mortality (%)**	**75th Percentile Mortality (%)**	**B**	***p***	**Exp (B) ***	**95% CI ^**
QTc Bazett °	422	406	438	0.45	1.71	0.817	<0.001	2.263	[1.822, 2.811]
QTc Fridericia °	410	397	424	0.73	1.43	0.481	<0.001	1.618	[1.296, 2.022]
QTc Framingham °	409	397	421	0.73	1.36	0.424	<0.001	1.528	[1.22, 1.913]
HR	72	64	82	0.65	1.71	0.880	<0.001	2.411	[1.944, 2.992]
Group 2 (46–65 Years): 50,284 Patients									
	Median	**25th Percentile**	**75th Percentile**	**25th Percentile Mortality (%)**	**75th Percentile Mortality (%)**	**B**	***p***	**Exp (B) ***	**95% CI ^**
QTc Bazett °	427	411	443	3.18	9.49	0.744	<0.001	2.105	[1.955, 2.266]
QTc Fridericia °	417	404	432	4.84	8.6	0.054	<0.001	1.716	[1.591, 1.85]
QTc Framingham °	416	404	429	5.33	7.91	0.434	<0.001	1.543	[1.43, 1.665]
HR	70	62	79	3.77	10.07	0.905	<0.001	2.472	[2.297, 2.659]
Group 3 (66–85 Years): 47,494 Patients									
	Median	**25th Percentile**	**75th Percentile**	**25th Percentile Mortality (%)**	**75th Percentile Mortality (%)**	**B**	***p***	**Exp (B) ***	**95% CI ^**
QTc Bazett °	435	418	454	16.69	35.54	0.618	<0.001	1.855	[1.787, 1.926]
QTc Fridericia °	425	410	442	20.40	33.58	0.472	<0.001	1.603	[1.544, 1.666]
QTc Framingham °	423	409	439	21.44	32.88	0.438	<0.001	1.550	[1.492, 1.611]
HR	70	62	80	18.76	34.37	0.607	<0.001	1.835	[1.768, 1.905]

° milliseconds, * relative risk/hazard ratio, ^ confidence interval.

Kaplan–Meier event-free survival curves in the whole population and in the three age-groups according to the 75th percentile/optimal operating points were also made, revealing the same significant trend in the whole population and in the three age-groups (see Figure S2 in Supplemental Materials).

Table 4 shows the multivariable forward Cox proportional hazard model, in the whole population and in the three age-groups, stratifying for sex, revealing the greater relative

risk of all-cause mortality for Bazett's correction and especially for the HR in the whole population and in all groups.

Table 4. Cox regression analysis in the entire population and in the three age-groups (group 1: 25–45 years; group 2: 46–65 years; and group 3: 66–85 years).

Whole Population				
	Cox B	**Cox Exp (B)**	**Cox 95% CI**	**Cox *p***
QTc Bazett °	0.400	1.492	[1.423, 1.564]	<0.001
QTc Fridericia °	0.166	1.181	[1.114, 1.252]	<0.001
QTc Framingham °	0.447	1.564	[1.473, 1.661]	<0.001
HR ^	0.519	1.681	[1.619, 1.745]	<0.001
Group 1 (25–45 Years)				
	Cox B	**Cox Exp (B)**	**Cox 95% CI**	**Cox *p***
QTc Bazett °	0.412	1.510	[1.107, 2.059]	0.009
QTc Fridericia °	0.019	1.019	[0.718, 1.446]	0.917
QTc Framingham °	0.201	1.222	[0.849, 1.761]	0.280
HR ^	0.729	2.072	[1.613, 2.662]	<0.001
Group 2 (46–65 Years)				
	Cox B	**Cox Exp (B)**	**Cox 95% CI**	**Cox *p***
QTc Bazett °	0.258	1.295	[1.164, 1.441]	<0.001
QTc Fridericia °	0.184	1.202	[1.057, 1.366]	0.005
QTc Framingham °	0.166	1.180	[1.034, 1.348]	0.014
HR ^	0.813	2.254	[2.076, 2.449]	<0.001
Group 3 (66–85 Years)				
	Cox B	**Cox Exp (B)**	**Cox 95% CI**	**Cox *p***
QTc Bazett °	0.259	1.296	[1.226, 1.369]	<0.001
QTc Fridericia °	0.069	1.071	[0.996, 1.153]	0.065
QTc Framingham °	0.269	1.309	[1.215, 1.410]	<0.001
HR ^	0.564	1.757	[1.686, 1.831]	<0.001

° milliseconds, ^ beats per minute.

4. Discussion

In this large non-selected adult population, the three considered QT correction methods (Bazett, Fridericia, and Framingham) were statistically associated with all-cause mortality, mainly in the whole population. However, the HR had, quite unexpectedly, the same or an even greater correlation with all-cause mortality, especially in younger subjects, compared to any QTc method (groups 1 and 2).

This population is heterogeneous and composed of acute and stable patients; the results are certainly influenced by the different clinical characteristic but remains significative in various clinical settings and in different age-groups.

For many years, clinicians corrected the QT interval based on the HR and researched the best QTc methods: therefore, it was somehow surprising that the simple evaluation of the HR performed equally or, sometimes, even better than the QTc.

Many studies already detected the association between the QTc and mortality, sometimes with controversial results: none identified the most predictive correction method, but some of them revealed the worst performance was from Bazett's method [16]. Vandemberk and coll. observed 6609 hospitalized patients and revealed that five QTc methods were related to mortality, but Bazett's correction had the worst performance; moreover, in a multivariable analysis, age, HR, and QTc were independent predictors of mortality, and, once more, Bazett's correction performed the worst [17].

Bazett's method, studied in 1920, is the oldest proposed for QT correction. It divides the QT interval by the square root of the RR interval and it is commonly used in clinical

practice despite the known over-correction at a fast HR and the under-correction at a slow HR; therefore, it should not be used for patients utilizing HR-modifying drugs [18,19].

In our study, Bazett's correction confirmed a lower independence from the HR but a stronger correlation with all-cause mortality with respect to Fridericia and Framingham methods. These results could not be easily explained, but the overestimation of the QTc through Bazett's method comprised a greater number of patients over the 75th percentile: the strength of this method could be represented by the overestimation of the QTc, especially with an HR increase.

Conversely, in a digital ECG re-examination of the Framingham population, Noseworthy and coll. observed that Bazett's method had a greater correlation with all-cause and cardiovascular mortality than other methods, but the association was attenuated after the adjustment for cardiovascular risk factors [20]. The authors suggested that the QTc contributed weakly to mortality, but reported an incremental risk with an increasing QTc. Also Yazdanpanah and coll. recently observed that, amongst five different QTc methods, Bazett's formula had the best correlation with cardiovascular mortality in 7071 non-hospitalised Iranian patients [21].

Our study confirms the results of Noseworthy and Yazdanpanah and the better prognostic value of Bazett's correction, in a twenty-fold larger population that included hospitalized and non-hospitalized patients. Therefore, the first practical message from our study is that clinicians should pay attention to QTc values that are greater than 440 msec in young subjects and greater than 455 msec in old subjects (over the 75th percentile in age-groups 1 and 3; see Table 3), keeping in mind that young females have longer QTc values compared to males [22]. In our study, mortality already increased from lower QTc values when compared to the QTc reference values [20,23].

Other relevant findings concern the HR. Meanwhile, the QTc and HR are obviously related but have different trends with increasing age: the QTc has a linear increase, while the HR has smaller and not-linear changes [22].

The HR is linked to genetics and lifestyle factors such as physical activity, diet, stress, and quality of sleep, and is influenced by cardiovascular diseases, infections, anemia, thyroid function, and using HR-modifying drugs [12–15]. The increase in the HR enhances oxygen consumption, imbalances the parasympathetic and sympathetic activity, provokes a faster progression of coronary diseases, reduces left ventricular function, increases the risk of ventricular arrhythmias, and increases inflammatory markers [2,24]. Despite all this evidence, an HR evaluation is not recommended in clinical guidelines for risk stratification.

In a recent meta-analysis, Zhang and coll. observed that an increase in resting HR greater than 10 beats per minute (bpm) raised the risk of all-cause and cardiovascular mortality, respectively, by 9% and 8% [25]. Likewise, Ristow and coll. observed an increased risk of all-cause mortality for a within-person increase in HR of greater than 2.8 bpm [26], while Aune and coll. reported an association between an at-rest HR increase of greater than 10 bpm and cardiovascular mortality, stroke, all-cause death, and cancer [27].

In general population studies, a resting HR higher than 90 bpm was described as potentially harmful and the probability of reaching age 85 was 40% lower in subjects with an HR greater than 80 bpm as compared with subjects with an HR lower than 60 bpm [28,29].

In conclusion, there is a large body of evidence showing that the HR is an independent predictor of mortality. Therefore, the second practical message from our study is that a simple evaluation of the HR may be equally important or even more important than a QTc evaluation, and that clinicians should consider a resting HR higher than 81 bpm as potentially harmful (75th percentile of the whole population and the three age-groups; see Table 3). It is worth noting that a resting HR of 81 bpm is currently held in the upper range of normality.

Despite this evidence, no human prospective studies demonstrated the efficacy, the risk–benefit ratio, or the cost-effectiveness of an HR-lowering treatment in a general population, even though, in patients with cardiovascular diseases (i.e., heart failure and coronary

heart diseases), the beneficial effects of lowering the HR on the symptoms and prognosis are well-known.

In any case, the precise definition of reference values for the HR and QTc is very difficult due to the multiplicity of confounding factors. As revealed by the low AUC in ROC curves, our study also showed difficulties in defining precise reference values, partly motivated by the heterogeneity of the enrolled population. Perhaps, the reference values should be further addressed and will be revisited and revised as more research data become available. In our population, we observed that a resting HR higher than 81 bpm and QTc values longer than 455 msec should be the focus, as they have a higher overall risk of mortality and clinicians should already reduce the use of QTc-modifying drugs from borderline values.

Due to its anonymous nature and the privacy policies applied by our institutions, this work has the following limitations: the precise prevalence of cardiovascular risk factors, cardiovascular diseases, and comorbidities; the unknown prevalence of patients utilizing QTc-modifying drugs and HR-modifying drugs; and the unknown exposure to environmental factors. For the same reason, we could not exactly collect the appearance of MACES and the specific causes of death.

5. Conclusions

The results of this study are interesting and obtained in a large real-word population comprising hospitalized and non-hospitalized patients. First of all, as revealed by previous studies, we observed that Bazett's QT correction better predicts all-cause mortality compared to other methods despite its lower independence from the HR. QTc values greater than 440 msec in young subjects and greater than 455 msec in old subjects should be considered potentially harmful. The evaluation of the HR at rest had the same or even greater prognostic value than the QTc. The HR is very simple to assess and clinicians should improve its evaluation with an alert for a resting HR above 81 bpm. However, both the QTc and HR have a great variability and depend on many confounding factors, so it is very difficult to define normal and pathological values, but the ECG is increasingly becoming a prognostic tool more than a diagnostic test.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/hearts5020015/s1, Figure S1: ROC curves for Bazett QTc (first column), Fridericia QTc (second column), Framingham QTc (third column), and HR (fourth column) in the whole population (first line), group 1 (second line), group 2 (third line), and group 3 (fourth line). In each panel, the red bullet represents the optimal operating point. Figure S2: Kaplan–Meier event-free survival curves according to the 75th percentile for QTc and for HR in the entire population and in the three age-groups (group 1: 25–45 years; group 2: 46–65 years; and group 3: 66–85 years). The dotted lines represent the 95% confidence interval. Table S1: Rates of mortality for the three QTc methods and for HR according to 25th and 75th percentile in the three facilities. Relative risk reveals the increased risk of all-cause mortality in subjects with a QTc and an HR above the 75th percentile.

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Data Availability Statement: The data underlying this article could be shared upon request from the corresponding author with the permission of the Health Authority and Services of Modena.

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