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Predictive value of TG/HDL-C and GFR-adjusted uric acid levels on cardiovascular mortality: the URRAH study

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Abstract

Background Insulin resistance (IR) and serum uric acid (SUA) are closely interconnected: SUA contributes to adversely affects the insulin signaling pathway and contributes to IR, while IR is a known predictor for the development of hyperuricemia. The triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) ratio has been proposed as an easily obtainable marker for IR. This research aimed to investigate the interaction between IR and glomerular filtration rate (GFR)-adjusted uricemia (SUA/GFR ratio) in determining CV risk in a large population cohort study.

Methods Data from 18,694 subjects were analyzed from Uric acid Right foR heArt Healt (URRAH) database. The study evaluated the association between TG/HDL-C ratio and SUA/GFR ratio, as well as their impact on the development of outcomes during the follow-up study period. The primary endpoint was CV mortality.

Results After a mean follow-up of 124 ± 64 months, 2,665 (14.2%) CV deaths occurred. The incidence of fatal and non-fatal CV events increased in parallel with the increase of TG/HDL-C quintiles. TG/HDL-C ratio showed a positive association with increasing of SUA/GFR ratio, even in non-diabetic patients. Multivariate analysis showed that the TG/HDL-C ratio increases the mortality risk even after adjustment for potential confounding factors. Finally, IR and GFR-adjusted hyperuricemia showed an additive effect on CV mortality.

Conclusions Both IR and SUA/GFR ratio independently predict CV mortality, regardless of age, gender, BMI, diabetes, hypertension and statin use. The joint effect of the TG/HDL-C ratio and the elevated SUA/GFR ratio was greater

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than the presence of each single risk factor on CV mortality. This highlights the importance of monitoring these markers to better assess cardiovascular risk.

Keywords TG/HDL-C ratio, Triglycerides, Insulin-resistance, Uric acid, Kidney function, Cardiovascular mortality

Introduction

Insulin resistance (IR), a state of systemic insulin sensitivity decline, is a key mechanism of lipid metabolism disorders. Accordingly, an abnormal lipid profile is an essential characteristic of patients with metabolic syndrome (MS), a condition strongly associated with the development of both type 2 diabetes and cardiovascular (CV) disease [1]. Hyperuricemia is also strongly associated with MS [2, 3], as well as with kidney disease progression, non-alcoholic fatty liver disease (NAFLD), hypertension, CV disease and mortality risk [4–7]. Moreover, IR and hyperuricemia are interconnected: serum uric acid (SUA) contributes to adversely affecting the insulin signaling pathway, while IR predicts the development of hyperuricemia [8–10]. The role of SUA in metabolic syndrome and its pleiotropic effects in multiple organ systems has been a matter of discussion due to its complex effects on cellular metabolism and signaling pathways [11, 12]. Some authors have proposed hyperuricemia as a component of MS, but little is known about its prognostic role in this contest.

Kidney function impairment plays a role in both IR and hyperuricemia, strongly conditioning the CV risk stratification. Chronic kidney disease (CKD) predisposes individuals to the development both of hyperuricemia [13] by reducing renal excretion of SUA, and to IR, secondary to chronic inflammation, oxidative stress, vitamin D deficiency, metabolic acidosis, anemia, and adipokine derangement which typically characterize CKD patients [14]. On the other side, IR promotes kidney disease [15] by several mechanisms, including worsening renal hemodynamics. Patients with MS have microvascular disease characterized by microalbuminuria, decreased glomerular filtration rate, tubular atrophy, interstitial fibrosis, and glomerulosclerosis [16]. IR causes endothelial dysfunction and generation of oxidative stress, which contributes to the deterioration of kidney function [17, 18]. This complex interplay between SUA, IR, and kidney function strongly impacts on CV mortality.

While the definition of MS is based on standard clinical and laboratory criterions, the definition of the IR in clinical practice is challenging. While hyperinsulinemic euglycemic clamp (HEC) is the gold standard for the assessment of IR, due to its complexity, this test is only used in small-scale research and not for population studies. Homeostasis model assessment of insulin resistance (HOMA-IR) requires an assessment of insulin levels, which is not practical in clinical practice in the community. Triglyceride/high-density lipoprotein (HDL) cholesterol ratio (TG/HDL-C) has been proposed as surrogate markers for predicting MS [18] and it has been proved to be a reliable sign for IR, endothelial dysfunction and preclinical organ damage [19–21]. In the clinical scenario, the TG/HDL-C has been estimated to be an adequate tool for IR assessment [22–24].

The Working Group on SUA and cardiovascular risk of the Italian Society of Hypertension had devised and set up the URRAH project (Uric Acid Right for Heart Health) to study the relationship between SUA and CVD [25]. Using this extensive, prognostic registry, the role of SUA levels in improving further risk stratification of patients with MS was investigated, demonstrating mild hyperuricemia significantly associated with an increased risk of CV mortality (CVM) in patients with MS, independently from other conventional CV risk factors [26]. In a recent sub-analysis of URRAH database, triglyceride-glucose index (TyG) thresholds are shown to be predictive of an increased risk of mortality, showing as several components of MS independently contribute to the risk of mortality [27–29].

Given that CV risk constitutes by far the leading cause of morbidity and mortality worldwide, it has become essential to investigate the role played by each key player in this context to reduce the heavy burden of global risk. The aim of this research was to explore the extent of interaction between IR and SUA/GFR ratio in determining CV mortality risk in a large population cohort study.

Methods

Database and study protocol

The URRAH project is a multicenter retrospective observational cohort study collecting data obtained from subjects aged 18 to 95 years. Participants are recruited within the epidemiological network of the Italian Society of Hypertension and include representation from almost all regions in Italy. The study protocol has been previously described in detail [23, 30].

For all subjects, a standardized set of items was recorded, including demographics, metabolic parameters, smoking habit, systolic and diastolic blood pressure (BP), renal function, history of CV, renal and cerebrovascular disease, concomitant treatments and outcome.

Kidney function was assessed by serum creatinine and GFR was estimated for each person using a standardized serum creatinine assay and the Chronic Kidney Disease Epidemiology Collaboration formula [24, 31].

Study outcomes included CV mortality as primary outcome and non-fatal events due to acute myocardial infarction, heart failure, or stroke as secondary outcomes. Diagnosis of events was obtained from hospital records or death certificates.

Ethics

The study data were collected either routinely or specifically for authorized studies. Participants did not undergo any additional tests or interventions, and their care or outcomes were not affected. The URRAH was performed according to the Declaration of Helsinki for Human Research (41stWorld Medical Assembly, 1990). The processing of the patients' personal data collected in this study complies with the European Directive on the Privacy of Data. All data to be collected, stored and processed are anonymized, and all study related documents are retained in a secure location. Personal information is not stored on individual local computers. Approval was sought from the Ethical Committee of the coordinating center at the Division of Internal Medicine of the University of Bologna (No. 77/2018/Oss/AOUBo). Informed consent was obtained from all subjects at recruitment.

Statistics

The patients' baseline clinical and demographic characteristics are reported as mean ± SD for continuous variables that are normally distributed and as median values (interquartile ranges) for variables that are skewed.

TG/HDL-C ratio was calculated according to the formula TG (mg/dL) divided by HDL-C (mg/dL) and the ratio was used as a continuous parameter, as a marker of insulin resistance. SUA/eGFR ratio was calculated according to the formula SUA (mg/dL) divided by eGFR (mL/min/1.73m^2) and the ratio was used as a continuous parameter.

Participants were grouped into TG/HDL-C quintiles, and statistical differences among groups were assessed using One-way ANOVA for normally distributed data and Kruskal–Wallis tests for non-normally distributed data. Comparisons of proportions among groups were made using the Pearson χ^2 test. Linear regression models were used to estimate the association between TG/HDL-C and SUA/GFR ratios. Logarithmically transformed values of skewed variables were employed for the statistical analysis.

TG/HDL-C and SUA/GFR ratios were used as independent variable in Cox analyses having fatal CV events as dependent variables, and sex, age, systolic BP, diabetes, hypertension, body mass index, and treatment with statins as possible confounders. Hazard ratios (HR) with 95% CI were produced. The null hypothesis was rejected for values of $p < 0.05$.

Kaplan Meier survival analysis was used to assess the event free survival in patients with different values of TG/HDL-C ratio, and with or without SUA/GFR above the median of values of the cohort. The analysis was adjusted for main confounding factors, i.e. diabetes and BMI.

Results

The main clinical characteristics of the entire study population, as well as when analyzed based on TG/HDL-C quintiles, are shown in Table 1. Altogether, out of 30,660 individuals, 18,694 for whom complete data on serum uric acid, GFR, triglycerides, HDL, and outcomes were available form the basis for the analyses.

Mean age was 57 ± 15 years, mean SUA was 5.03 ± 1.42 mg/dl and mean GFR was 82 ± 20 ml/min per 1.73 m^2, 46.7% were males, 67.2% had a history of hypertension and 10.5% of diabetes.

Data reported in Table 1 show some relevant differences among TG/HDL-C subgroups. Increasing values of age, BMI, intima media thickness (IMT), systolic blood pressure (SBP), and hypertension prevalence were observed progressively with rising IR, expressed as TG/HDL-C levels. Conversely, the mean eGFR decreased progressively as IR increased, going from 89 mL/min/1.73m^2 in the lower TG/HDL-C quintile to 78 mL/min/1.73m^2 in the upper TG/HDL-C quintile ($p < 0.0001$). As expected, glycemia and proportion of diabetes rose along with the increase in TG/HDL-C quintiles, as a surrogate of IR (Table 1).

The behavior of the association between SUA/GFR ratio and the TG/HDL-C ratio is shown in Supplemental Fig. 1. The surrogate of IR was directly associated to SUA/GFR in the whole cohort (data not shown, β = 12.5 [95% CI 11.7 to 13.4], $p < 0.0001$), and both in diabetic (Figure S1B, β = 5.6 [95% CI 3.0 to 8.2], $p < 0.0001$) and non-diabetic patients (Figure S1A, β = 13.5 [95% CI 12.6 to 14.4], $p < 0.0001$).

Over a median follow-up of 10.4 ± 5.3 years, 1,394 (7.5%) CV deaths were recorded, including 395 (2.2%) fatal myocardial infarction, 339 (1.9%) fatal cerebrovascular events, and 398 (2.6%) fatal heart failures.

As shown in Table 2, our analysis delved into the incidence of CV events and mortality within patient groups stratified on the basis of TG/HDL-C quintiles. Remarkably, an ascending pattern in the prevalence of primary and secondary outcomes corresponded to increasing IR quintiles ($P < 0.0001$).

Table 1 Demographic and clinical characteristics in patients on the basis of TG/HDL-C quintiles

	All	*TG/HDL-C* 1° quintile	*TG/HDL-C* 2° quintile	*TG/HDL-C* 3° quintile	*TG/HDL-C* 4° quintile	*TG/HDL-C* 5° quintile	*p*
N	18,694	3778	3728	3676	3649	3863	
Age, years	57 ± 15	54.3 ± 16.1	57.9 ± 15.5	58.6 ± 14.9	59.2 ± 14.0	58.3 ± 13.5	< 0.0001
Male gender, %	46.7	40	45.4	48.2	47.8	52.1	< 0.0001
BMI, kg/m2	26.7 ± 4.3	24.6 ± 4.0	26.0 ± 4.2	26.7 ± 4.2	27.6 ± 4.2	28.4 ± 4.1	0.021
Smoke, %	24.1	17.4	21.2	22.2	24.9	29.6	< 0.0001
Exercise, %	55.4	45.1	45.3	41.1	41	39.2	< 0.0001
Hypertension, %	67.2	56.9	66.4	67.7	72.1	72.4	< 0.0001
SBP, mmHg	143.4 ± 23.7	138.2 ± 24.1	143.6 ± 24.4	144.2 ± 23.7	146.2 ± 23.4	145.6 ± 23.0	0.004
DBP, mmHg,	85.3 ± 12.8	83.0 ± 12.6	84.9 ± 12.7	85.1 ± 12.7	85.9 ± 13.2	86.5 ± 12.9	0.046
HR, bpm	71.9 ± 12.3	71.4 ± 11.8	72.6 ± 12.8	72.2 ± 12.4	72.4 ± 11.7	72.8 ± 12.2	< 0.0001
Creatinine, mg/dl	0.93 ± 0.26	0.85 ± 0.21	0.90 ± 0.20	0.92 ± 0.23	0.95 ± 0.22	0.98 ± 0.28	< 0.0001
GFR, ml/min per 1,73m²	82.1 ± 19.6	89.0 ± 19.5	83.4 ± 19.7	81.5 ± 19.2	79.1 ± 19.2	78.0 ± 19.5	< 0.0001
Uric acid, mg/dl	5.03 ± 1.42	4.37 ± 1.20	4.72 ± 1.35	4.93 ± 1.31	5.25 ± 1.35	5.67 ± 1.48	< 0.0001
Gout, %	1.06	0.13	0.59	0.73	1.55	2.3	< 0.0001
Allopurinol use, %	1.47	0.41	0.69	1.32	1.85	2.41	< 0.0001
Glucose, mg/dl	98.6 ± 25.2	91.7 ± 16.9	95.8 ± 20.9	98.2 ± 23.7	101.2 ± 27.4	106.1 ± 32.9	< 0.0001
Diabetes, %	10.5	5.1	7.1	8.8	11.8	15	< 0.0001
Total Cholesterol, mg/dl	212.2 ± 39.4	201.4 ± 37.6	207.3 ± 38.6	212.6 ± 39.3	217.8 ± 38.5	222.9 ± 39.5	0.043
HDL-cholesterol, mg/dl	52.9 ± 14.9	68.3 ± 14.1	58.3 ± 11.8	51.9 ± 10.6	46.8 ± 9.1	39.2 ± 8.8	< 0.0001
LDL-cholesterol, mg/dl	134.4 ± 35.9	120.8 ± 33.3	131.8 ± 34.1	139.1 ± 34.9	143.3 ± 34.8	137.7 ± 37.8	< 0.0001
Triglycerides, mg/dl	128.7 ± 78.8	62.2 ± 15.7	87.2 ± 18.6	109.2 ± 23.0	140.8 ± 23.3	234.2 ± 100.2	< 0.0001
Triglycerides/HDL-C ratio	2.77 ± 2.37	0.92 ± 0.21	1.50 ± 0.16	2.11 ± 0.20	3.02 ± 0.35	6.20 ± 3.13	< 0.0001
SUA/GFR ratio	0.067 ± 0.038	0.053 ± 0.027	0.062 ± 0.033	0.067 ± 0.035	0.073 ± 0.036	0.080 ± 0.048	< 0.0001
IMT, mm	1.21 ± 0.72	1.08 ± 0.61	1.07 ± 0.55	1.26 ± 0.82	1.34 ± 0.83	1.40 ± 0.79	< 0.0001
Diuretics, %	16.5	10.5	14.3	15.7	19.8	20.6	< 0.0001
Statins, %	5.3	3.6	5.2	5.8	6.3	5.5	< 0.0001
RAAS inhibitors, %	1.6	1.1	1.5	1.2	1.7	1.5	0.28

Abbreviations: *BMI* body mass index, *CI* confidence interval, *GFR* glomerular filtration rate, *HDL-C* high-density lipoprotein cholesterol, *HR* hazard ratio, *TG* triglycerides, *SUA* serum uric acid

Table 2 Cardiovascular and overall outcomes in patients on the basis of TG/HDL-C quintiles

	ALL	TG/HDL-C 1° QUINTILE	TG/HDL-C 2° QUINTILE	TG/HDL-C 3° QUINTILEE	TG/HDL-C 4° QUINTILE	TG/HDL-C 5° QUINTILE	*p*
N	18,694	3778	3728	3676	3649	3863	
ALL CAUSE MORTALITY, %	14.2	10.9	14.8	15.8	16.2	17	< 0.0001
NON FATAL MI, %	2.2	0.7	1.4	2.1	2.7	3.5	< 0.0001
FATAL MI, %	2.2	1.5	1.9	2.3	2.4	3.1	< 0.0001
NON FATAL CBV EVENTS, %	1.8	0.7	1.4	1.7	2.4	2.8	< 0.0001
FATAL CBV EVENTS, %	1.9	1.6	2.2	1.8	1.8	2	0.477
NON FATAL HEART FAILURE, %	1.4	0.7	1.1	1.7	1.7	1.9	< 0.0001
FATAL HEART FAILURE, %	2.6	1.6	2.9	3	3	2.5	< 0.0001
CV MORTALITY, %	7.5	4.9	7.2	7.6	8.5	9	< 0.0001

Abbreviations: *CBV* cerebro-vascular events, *CV* cardiovascular, *MI* myocardial infarction

A Cox regression interaction analysis using the primary outcome assessed the interaction between TG/HDL-C and SUA/GFR ratio in determining CV mortality ($p < 0.0001$, data not shown).

Consistently, increased risk of CV mortality was observed along with increasing quintiles of TG/HDL-C, even after adjustment for the potential confounding

factors, such as SUA/GFR ratio, renal function, BMI and the presence of diabetes (Fig. 1).

Both TG/HDL-C ratio and SUA/GFR ratio were independently associated to CV mortality in multivariable Cox regression models (Table 3). Being in the 4° or 5° quintile of TG/HDL-C led to a 20 and 37% increased risk of CV mortality (HR 1.20, 95% CI, 1.00–1.25, $P=0.05$ and HR 1.37, 95% CI, 1.13–1.65, $P=0.001$), respectively (Table 3).

The Kaplan–Meier curves for CV mortality on the basis of SUA/GFR ratio above or below the median) and TG/HDL-C in the lowest (1°–3°) or highest (4°–5°) quintiles are shown in Fig. 2. In particular, participants with a higher SUA/GFR ratio or higher TG/HDL-C ratio had a significantly greater likelihood of cardiovascular mortality compared to those without these risk factors. Those patients with both higher SUA/GFR ratio and higher TG/HDL-C ratio had a significantly higher probability of CV mortality than those with only one risk factors, independently by the presence of diabetes and BMI (log-rank test: $P<0.0001$).

Cox-regression analysis confirmed the predictive role of the presence of one or both the two risk factors, which showed a higher risk of CV mortality in participants with SUA/GFR ratio above the median and TG/HDL-C ratio belonging to the 4° and 5° quintiles (HR: 1.68, 95% CI: 1.42–1.99). This predictive role was still observed even after accounting for the main potential confounding factors (Table 4).

Discussion

Since hyperuricemia, dyslipidemia, and IR are all modifiable risk factors contributing to the progression of atherosclerosis and CV disease, understanding the relative contribution of each component on CV risk is of interest. Although all these risk factors have been investigated in large population studies, few analyses have examined their joint effect as commonly observed clinical traits [32–34].

This study explored the impact of TG/HDL-C, an easily obtainable and reliable marker of IR, on CV mortality risk in a high-risk population cohort. Using multivariate Cox regression analysis, we found both TG/HDL-C ratio and SUA/GFR ratio significantly predict CV mortality in high-risk population, regardless of other interconnected risk factors, including age, gender, diabetes, hypertension, BMI and statin treatment. Moreover, we found an additive (but not synergistic) effect of IR and GFR-adjusted SUA levels on CV mortality risk.

As expected, along with the rise in TG/HDL-C, we observed a progressive increase in age, BMI, SUA levels and prevalence of gout, hypertension and diabetes. Conversely, renal function decreases as IR increases (Table 1). The TG/HDL-C ratio has recently been proposed as a novel biomarker for predicting the risk of both MS and CV disease [35, 36], as well as a useful tool for monitoring and assessing the risk of CKD progression [37]. In fact, it has been shown to predict both a low GFR and the occurrence of micro/

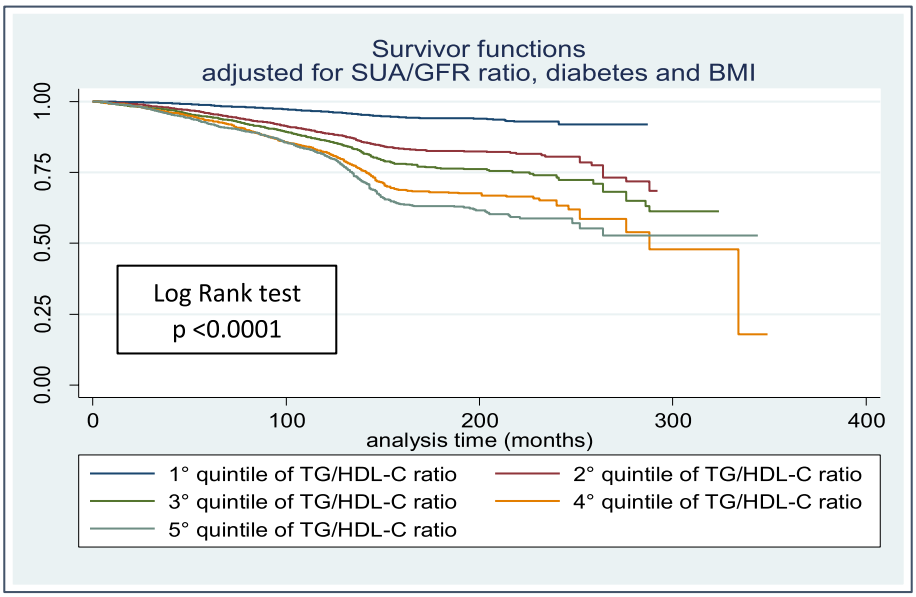

Fig. 1 Kaplan–Meier survival curves for cardiovascular mortality according to TG/HDL-C quintiles adjusted for SUA/GFR ratio, diabetes and body mass index (BMI). Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; SUA, serum uric acid

Table 3 Cox regression univariate and multivariate analysis for cardiovascular mortality including SUA/GFR ratio and TG/HDL-C quintiles

	UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS (MODEL 1)			MULTIVARIATE ANALYSIS (MODEL 2)		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Age, years	1.12	1.11–1.12	< 0.0001	1.11	1.10 – 1.11	< 0.0001	1.30	1.17 – 1.45	< 0.0001
Gender, male	1.02	0.91–1.13	0.767	1.30	1.17 – 1.45	< 0.0001	1.11	1.10 – 1.11	< 0.0001
BMI, Kg/m^2	1.01	1.00–1.03	0.025	0.98	0.96 – 0.99	0.001	0.98	0.96 – 0.99	< 0.0001
SUA/GFR, (logarithm)	3.74	3.36–4.15	< 0.0001	1.51	1.32 – 1.71	< 0.0001	1.52	1.33 – 1.73	< 0.0001
Diabetes (the presence of)	3.81	3.37–4.30	< 0.0001	1.99	1.75 – 2.27	< 0.0001	1.79	1.63 – 1.97	< 0.0001
Hypertension (the presence of)	2.28	2.00–2.61	< 0.0001	1.09	0.95– 1.25	0.213	1.09	0.95– 1.25	0.123
Statins, treatment	0.50	0.35–0.73	< 0.0001	0.23	0.16 – 0.33	< 0.0001	0.23	0.16 – 0.33	< 0.0001
TG/HDL-C (logarithm)							1.15	1.05 – 1.26	0.027
TG/HDL-C (1° quintile)	REF			REF					
TG/HDL-C (2° quintile)	1.45	1.21–1.75	< 0.0001	1.13	0.93–1.37	0.204			
TG/HDL-C (3° quintile)	1.51	1.26–1.82	< 0.0001	1.15	0.95–1.39	0.148			
TG/HDL-C (4° quintile)	1.71	1.43–2.05	< 0.0001	1.20	1.00–1.45	0.050			
TG/HDL-C (5° quintile)	1.79	1.50–2.14	< 0.0001	1.37	1.13–1.65	0.001			

Model 1 includes TG/HDL-C ratio quintiles, Model 2 includes TG/HDL-C expressed as continuous variable

Abbreviations: *BMI* body mass index, *CI* confidence interval, *GFR* glomerular filtration rate, *HDL-C* high-density lipoprotein cholesterol, *HR* hazard ratio, *TG* triglycerides, *SUA* serum uric acid

macroalbuminuria, even in non-diabetic patients [38]. Although the TG/glucose index (TyG) has also been proposed as surrogate marker for IR, its role is even less defined at this time. Accordingly, in a longitudinal study with a relatively small sample size ($n = 732$), the multivariable-adjusted hazard ratios (HR) for incident CV disease were statistically significant when evaluated by the TG/HDL-C ratio, but not by the TyG index [39]. The largest European study investigating the predictive role of TG/HDL-C ratio is a recent longitudinal analysis from 403,335 participants from UK Biobank which showed as the association between the TG/HDL-C ratio and increased risk for CV disease was largely mediated by a greater prevalence of dyslipidemia, type 2 diabetes, and hypertension [40]. Our findings of a strong association between higher TG/HDL-C levels and a greater risk for incidence of CV events (Table 2) confirm and extend previous studies showing that TG/HDL-C is a reliable marker for coronary atherosclerosis also in healthy non-diabetic individuals [41]. In line with the observation of a parallel increase in TG/HDL-C ratio and intima media thickness at the carotid level in the baseline picture of our study population (Table 1), elevated TG/HDL-C was found to predict unfavorable progression of arterial stiffness in a prospective cohort of hypertensive patients [42].

An important result, to our knowledge, which has not been previously reported, is the great impact of IR (expressed as TG/HDL-C) on CV mortality, independently by kidney function, SUA levels, BMI and diabetes (Table 3, Fig. 2). IR is known to be an important mediator of the association between SUA and vascular stiffness [43, 44], even in non-diabetic patients [45, 46]. In this study, we report a gradual increase in CV risk with incremental exposure to increasing quintiles of the TG/HDL ratio, independently by major confounding factors of IR, such as diabetes and BMI (Fig. 1).

The relationship between SUA/GFR and IR is further complicated for several reasons. First, the relationship between SUA and kidney function must be considered. SUA levels are highest in CKD patients due to impaired renal excretion, and the detrimental effects of SUA on kidney function [47, 48], as well as on vascular disease [43, 49–53], have been well documented. Evidence is accumulating regarding the need to index SUA to renal function [54, 55]. Previous studies have investigated the role of the serum creatinine (sCr)-normalized SUA (SUA/sCr) ratio in various contexts [56–60], identifying a threshold value of this index to predict CV mortality [56]. Interestingly, a significant positive correlation between SUA/Cr and metabolic syndrome has been reported in the Chinese population, suggesting it may be a novel predictive marker for metabolic syndrome risk [61].

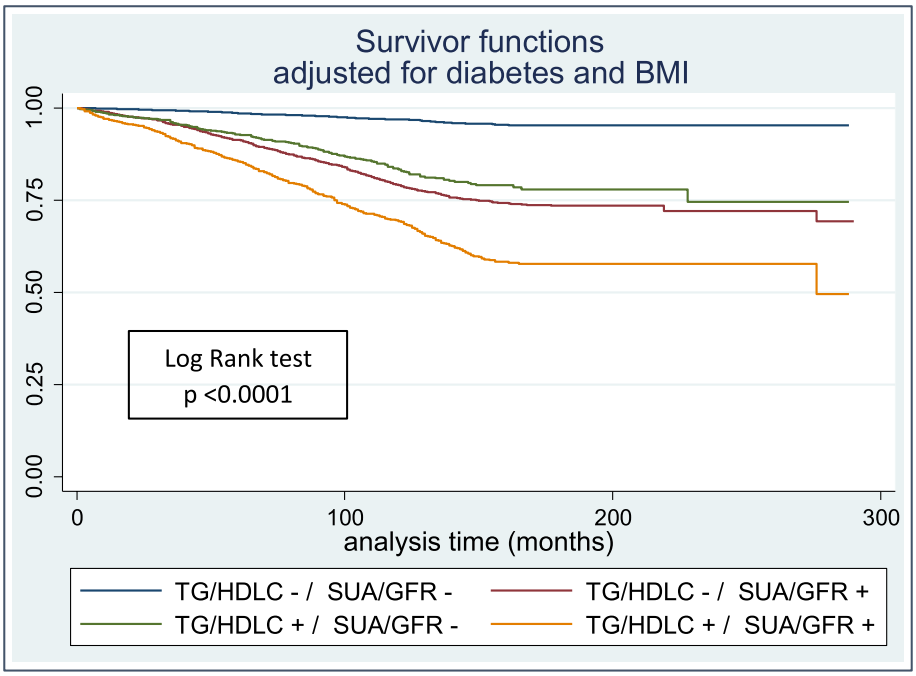

Fig. 2 Kaplan–Meier survival curves for cardiovascular mortality according to SUA/GFR ratio (above or below the median) and TG/HDL-C quintiles (1°–2°–3° vs 4°–5° quintiles) adjusted for the presence of diabetes and body mass index (BMI). Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; SUA, serum uric acid

Table 4 Cox regression multivariate analysis for cardiovascular mortality including the combined effect of TG/HDL-C ratio ≥ 4°quintile and SUA/GFR ratio ≥ median

MULTIVARIATE ANALYSIS			
	HR	**95% CI**	***P* value**
Age, years	1.10	1.09–1.11	< 0.0001
Gender, male	1.27	1.14–1.42	< 0.0001
BMI, Kg/m2	0.97	0.97–0.99	0.003
Diabetes (the presence of)	1.87	1.65–2.12	< 0.0001
Hypertension (the presence of)	1.09	0.95– 1.25	0.123
Statins, treatment	0.25	0.17–0.36	< 0.0001
SUA/GFR < median TG/HDL < 4° quintile	reference		
SUA/GFR ≥ median TG/HDL < 4° quintile	1.44	1.22–1.70	< 0.0001
SUA/GFR < median TG/HDL ≥ 4° quintile	1.58	1.28–1.96	< 0.0001
SUA/GFR ≥ median TG/HDL ≥ 4° quintile	1.68	1.42–1.99	< 0.0001

Abbreviations: *BMI* body mass index, *CI* confidence interval, *GFR* glomerular filtration rate, *HDL-C* high-density lipoprotein cholesterol, *HR* hazard ratio, *TG* triglycerides, *SUA* serum uric acid

A second point concerns the role of uric acid. SUA, while a major antioxidant in human plasma, is paradoxically linked to the development of obesity, hypertension, and CV disease—conditions associated with oxidative stress. This paradox may stem from uric acid acting as an antioxidant in plasma but as a pro-oxidant within cells. Evidence suggests that its pro-oxidative effects play a contributory role in the pathogenesis of CV disease and mortality risk. Nonetheless, the GFR estimate, taking into account gender, age and ethnicity is overall the best index of renal function, especially for large-scale use [62]. For this reason, in order to analyze the role of an increase in SUA levels due to altered uric acid production independently by the increased levels resulting from reduced renal excretion, we assess the role of SUA/GFR ratio in determining CV mortality risk. In this way, we aim to describe the unfavorable impact of uric acid overproduction independently by the detrimental effect of impaired renal function on CV outcome.

While the relationship between IR surrogates and CVD outcomes have been extensively investigated [63], even in non-diabetic patients [64], an assessment of the interplay between IR, SUA levels and kidney function in predicting CV risk in a community-based populations was lacking.

IR is a central component of the metabolic dysregulation observed in obesity, increasing the risk of developing

type 2 diabetes and complications related to diabetes such as CKD [65–67]. Once again, the confounding factors are interrelated. In this study, the risk of CV mortality was significantly higher in participants with a higher TG/HDL-C ratio, independent of confounding factors (Table 3, $p=0.027$). A previous URRAH analysis showed that SUA can predict both CV and all-cause mortality in patients without established cardiovascular disease, independently of TG levels [68]. The relationship between SUA levels and lipids, and their interaction in relation to prognosis were explored in specific settings [69–71]. In contrast, investigating the predictive role of SUA/GFR ratio and of a surrogate marker of IR in their potential interplay is novel in this context. We confirm the TG/HDL-C predictive power for CV mortality, reporting that TG/HDL-C ratio between 2.5 and 3.8 (4° quintile), and > 3.8 (5°quintile) increased CV mortality risk by 20 and 37%, respectively, independently by age, gender, SUA levels, kidney function, BMI, the presence of hypertension, diabetes and statins treatment (Table 3, $p=0.05$ and $p=0.001$, respectively). Moreover, no studies have explored the predictive role of SUA/GFR concerning CV mortality risk across TG/HDL-C strata.

The strength of the study shown herein is that, to our knowledge, it is the first aimed at reporting for the first time the potential interplay between these two factors, demonstrating an independent and additive effect on CV mortality risk (Fig. 2, Table 3 and 4). The limitations are represented by the fact that this was a retrospective evaluation, that the analysis was based on a single TG, HDL-C and SUA measurements without taking into consideration the dilution bias, and that the design was fit to demonstrate an association but not a causality in the relationship between TG/HDL-C, SUA and CV mortality. Another significant limitation is the inability to assess the muscle mass, which may represent a limitation in estimating GFR.

Conclusions

Our results provide substantial evidence for the TG/HDL-C ratio as an indicator of CV risk, independent of SUA levels and kidney function. This reinforces its importance as a useful and cost-effective early indicator for subclinical atherosclerosis and subsequent cardiac and cerebrovascular events, with significant implications for global health. The TG/HDL-C is a readily available measure that can be used in the future to predict CV mortality in clinical or epidemiological settings. For the first time, we assessed the impact of SUA/GFR ratio on CV mortality risk and described the additive effect of GFR-adjusted SUA levels and the TG/HDL-C ratio on CV risk. The implications of elevated TG/HDL-C in subjects with increased SUA compared to those with normal SUA, as well as in CKD and non-CKD patients, warrant further investigation and may shed light on the pathophysiology of IR and its consequences.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-025-02440-w.

Supplementary Material 1.

Authors' contributions

FV, RP, CB: Conceptualization, EC, GD, GG,CF, MLM, GP, AV: Methodology, FA, CMB, BB, MB, FC, RC, MC, AFGC, MM, AM, PN, PP: Data curation, ER, FV; RP: Writing- Original draft preparation. MC, PC, LD, FG, LG, CG, GI, EI, LL, AM, SM: Visualization, Investigation. EC, GD, GG, GP, AV: Supervision. FQT, MR, GR, GR, MS, VT, GT, AU, PV: Validation. All authors reviewed the manuscript.

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Data availability

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The URRAH project was performed according to the Declaration of Helsinki for Human Research (41stWorld Medical Assembly, 1990). The processing of the patients' personal data collected in this study complies with the European Directive on the Privacy of Data. Approval was sought from the Ethical Committee of the coordinating center at the Division of Internal Medicine of the University of Bologna (No. 77/2018/Oss/AOUBo). Informed consent was obtained from all subjects at recruitment.

Competing interests

The authors declare no competing interests.

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