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Investigation serum uric acid in cardiovascular mortality and all-cause mortality men and women in AL-Muthanna province-Iraq

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ABSTRACT

The aim of the study was to investigate whether a serum uric acid increase or decrease in cardiovascular mortality (CVM) and all-cause mortality (ACM) in Iraqi populations women and men. Once this was accomplished, the objective was to diagnose pertinent in both CVand AC mortality. The study has been included 235 patients who underwent were divided into groups ACM and CVM that distributed 135 and 100 respectively between June 2016 to June 2018. The primary funding was a composite accident ACM that included type2diabetes (T2D) and chronic kidney disease (CKD) and CVM. This investigation has been carried out by using SPSS version22. The investigation developing a uric acid in ACM was higher more than CVD mortality. Elevated uric acid was p-value 0.145 in ACM and 0.74 in CVM. In males have been recorded more than in females in ACM and CVM, also increased uric acid value when progressing age in both genders and groups. In this study shows to present increase cardiovascular in male more than female mortality and noted elevated uric acid to increase age patients in both CVM and All-cause mortality**.** Uric acid was linked with an increase risk ACM and CVM in women and men. Uric acid was found as a significant influence in ACM and CVM.

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INTRODUCTION

Uric acid has been demonstrated during the 19th century and associated with many diseases, all-cause mortality (ACM) and cardiovascular mortality (CVM) that covered T2D and CKD (Davis, N.S., 1897) and therefore considered a marker for these diseases. In general, uric acid makes in liver and excretion in the kidney (Chaudhary, K 2013 and Kutzing, M.K.2008) and is a terminus product of oxidation of xanthine and hypoxanthine in nucleotide metabolism (Sluijs, I *et al.,* 2012). UA is a $C_5H_4N_4O_3$ (7, 9-dihydro-1H-purine-2, 6, 8 (3H) - trione) heterocyclic organic complex with a molecular weight of 168 Dalton. A lot of enzymes are played a role in the diversion of the two purine nucleic acids, adenine and guanine, to UA (Maiuolo, J. *et al.,* 2015). The normal value of serum UA level is<420 mmol/l (<7 mg/dl) in men and <350 mmol/l (<6 mg/dl) in women (Ruilope, Luis Miguel *et al.,* 2001). There are large quantity constructive in patients CVD morbidity (Fang, J *et al.,* 2000). Elevated high-sensitivity C-reactive protein (hs-CRP) level hyperuricemic patients, the hs-CRP level was found to be an independent prognostic of homeostatic model evaluation insulin resistance (Kelly, C.C. *et al.,* 2001and) Festa, A., *et al.,* 2000). In diabetics soluble uric acid could increase tissue levels of Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and the generation of reactive oxygen species (ROS) in mature adipose tissue (Sautin, Y.Y. *et al.,* 2007). The oxidation stress that occurs in adipose tissue reveals decrease sensitivity to insulin as a risk factor of insulin resistance. Despite, the reasoning mechanism of hyperuricemia in insulin resistance is still not apparent (Zhu, Y., Hu, Y., *et al.,* 2014).

Concern about increase uric acid has become a central issue for these diseases and as a result much research in recent years has focused on this problem and described treatment increase UA which associated with these diseases but the drug occur overlap with these infections (Yang, T.Y., *et al.,* 2015), and researchers are Consensual on treatment of UA is lacking (Soltani, Z. *et al.,* 2013). Although many previous studies had found a significant association between SUA level in both ACM and CVM, it is still not known and controversial whether it is an independent causative mechanism in the development of CAD or dependent on the presence of the other cardiovascular risk factors (CRFs). (Gagliardi, A.C. *et al.,* 2009).

Recent studies confirmed that Hyperuricemia has been reached to hyperinsulinemia in metabolic syndrome and decrease UA when excretion in kidney, and is not admitted as a main mediator of metabolic syndrome, kidney disease, and cardiovascular disease revolution (Soltani, Z., *et al.,* 2013), the researcher (Tseng, W.C., *et al.,* 2018) has demonstrated value SUA between (4 to <8 mg/dl) in older associated with CVM. Also, this study (Jin, Y.L. *et al.,* 2013) has referred the correlation between UA and cardiovascular risks are noted not only with hyperuricemia but also with UA levels in average value and this study (Culleton, B.F. *et al.,* 1999) increase UA not associated CVD. Furthermore, no study has been carried out in the Iraqi population in AL-Muthanna province. The aim of the study to investigate the correlation between serum uric acid SUA level and among different diseases for patients input in these hospitals.

SUBJECTS AND METHODS

Study population

AL-Muthanna province located in the south of Iraq. The enumeration community is approximately 800, 000 individuals. Elevated incidence ratio diseases CVM in this province because they are eating a lot of food that included on lipid, salt and sugar that lead prevalence obesity, diabetes and hypertension are associated with prevalence CVD. This city Included 3 hospitals AL Hussian teaching, AL Khider and AL Rumaitha teaching hospital. The current investigation involved sampling was collected from those hospitals in AL-Muthanna province between January 2017 and June 2018. All patients aged more than 40years old and recorded information that was obtained from all patients and dealt with it in strict secrecy. Data were allowing the determination of the status SUA level in 235 patients in those hospitals. This number has been distributed 72 and 55 men ACM and CVM respectively and 63 and 45 women ACM and CVM respectively. The study has been agreed by the medical ethics committee in those hospitals. All participants were previously diagnosed and provided written informed consent.

Data collection

In this survey, all patients underwent to work some laboratory analyses demographics including sex, age, body mass index (BMI), systolic and diastolic blood pressure (SBP and DBP), medical history for participants that related with CVD, CKD andT2D and drug agents were obtained in this data. At the commencement of Heart Revival Center (HRC), the height and weight were recorded for every patient and BMI computed this way.

Research facility parameters were acquired from routine month to month mid-week venous blood tests. They included uric acid, total cholesterol (TC), triglycerides (TG), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C) and high-sensitivity C-reactive protein (hsCRP).

Statistical analysis

The data were analysed using the SPSS version 22 for Windows (SPSS, Chicago, IL, USA). The mean of the data was assessed by one-way ANOVA and t-test. Moreover, frequency results were analyzed by Pearson chi-square and Fisher's exact test. Differences were considered statistically significant at $P<0.05$

RESULTS

Among the investigation patients, there were 108 (46 %) women and 127 (54 %) men. Their ages were between 40-79 years old, in table 1 showed distribution parameters value into ACM.

DISCUSSION

Uric acid is a considered as a maker for predictive value in both ACM and CVM and others biomarker that utilized in this study and found an increased

risk ACM and CVM (Mantovani, A. *et al.,* 2018). This list of the analyses are not exhaustive, but a few biomarkers were a strong relationship with CVM such as high lipoprotein (HDL) (Patterson, C.C. *et al.,* 2015). Some recent investigation has been indicated role SUA evolution of ACM and CVM (Lin, G.M. *et al.,* 2015 and Nakamura, S., *et al.,* 2017). Epidemiological evidences have noted that significant UA amount was an independent risk factor CVD (Okura, T. *et al.,* 2009 and Beevers, D.G., *et al.,* 1998) and others risk factors mortality (Kawai, T. *et al.,* 2012 and Panero, F., *et al.,* 2012) have been suggested an item of the metallic syndrome. Recent reviews have also proven that increase UA independently predicted CVM (Kim, S.Y. *et al.,* 2009 and Feig DI., *et al.,* 2008).

Table 1: Distribution of the studied parameters values according to the gender of All-cause mortality patients

Parameters	All-cause mortality		P value
	Female	Male	
DBP, mm Hg	86.6±3.9	87.4±3.9	0.233
SBP, mm Hg	134.5±9.1	137±9	0.111
HDL, mmol/L	1±0.32	1.2±0.34	0.008*
LDL, mmol/L	5.2±0.65	5.4±0.56	0.135
TC, mmol/L	6±0.3	5.7±0.35	0.000*
hs-CRP mg/L	2.48±1.5	2.31±1.8	0.569
CRP mg/L	0.99±0.6	0.74±0.4	0.007*
BMI kg/m2	24.9±1.8	25.26±2.2	0.371
Uric Acid	5.6±1.9	6±1.6	0.145

* represents a significant difference at $P \leq 0.05$. Data are expressed as Mean±SD.

Regarding gender groups (female and male), the studied parameters were distributed and statistically analyzed. The results showed a significant difference $p<0.05$ for HDL, TC and CRP parameters between female and male groups, where p values are 0.008, 0.000, 0.007; respectively. The results of other studied parameters (DBP, SBP, LDL, hs-CRP, BMI and UA) showed no significant difference, where $p>0.05$.

Table 2: Distribution of the studied parameters values according to the gender of Cv mortality patients

	Cv mortality		
	Female	Male	
DBP, mm Hg	85.4±3.2	85.8±3.4	0.578
SBP, mm Hg	138.2±8.9	142.3±6.9	0.012*
HDL, mmol/L	1.12±0.3	1.32±0.33	0.003*
LDL, mmol/L	5.54±0.7	5.55±0.6	0.967
TC, mmol/L	5.8±0.6	6.2±0.6	0.001*
hs-CRP mg/L	2.49±2	2.33±1.9	0.702
CRP mg/L	0.56±0.3	0.77±0.4	0.013*
BMI kg/m2	25.28±2.7	27.9±2.4	0.000*
Uric Acid	5.4±1.86	6.1±1.83	0.074

* represents a significant difference at $P \leq 0.05$. Data are expressed as Mean±SD.

Regarding cv mortality, the studied parameters were distributed according to gender groups (female and male) and statistically analyzed. The results revealed a significant difference $p<0.05$ for SBP, HDL, TC, CRP and BMI parameters between female and male groups, where p values are 0.012, 0.003, 0.001, 0.013, 0.000; respectively. The results of other studied parameters (DBP, LDL, hsCRP and Uric acid) showed no significant difference, where $p>0.05$.

Table 3: Comparison of the studied parameters means between All-cause mortality group and CV mortality groups of patients

Parameters	All-cause mortality	CV mortality	P value
DBP, mm Hg	87±3.9	85.6±3.3	0.002*
SBP, mm Hg	135.9±9.12	140.5±8.15	0.000*
HDL, mmol/L	1.15±0.34	1.23±0.33	0.06
LDL, mmol/L	5.36±0.6	5.55±0.67	0.031*
TC, mmol/L	5.9±0.37	6±0.7	0.044*
hs-CRP mg/L	2.39±1.69	2.4±2	0.942
CRP mg/L	0.86±0.5	0.67±0.4	0.003*
BMI kg/m2	25.1±2	26.7±2.8	0.000*
Uric Acid	5.86±1.7	5.81±1.8	0.849

* represents a significant difference at $P \leq 0.05$. Data are expressed as Mean±SD.

This table illustrates the general Comparison between All-cause mortality group and CV mortality groups for all the studied parameters. The results showed a significant difference $p<0.05$ for DBP, SBP, LDL, TC, CRP and BMI, where p values are 0.002, 0.000, 0.031, 0.044, 0.003, 0.000; respectively. The results of other studied parameters (HDL, hsCRP and Uric acid) showed no significant difference, where $p>0.05$.

Table 4: Distribution of the studied parameters values according to the age of All-cause mortality patients

Parameters	All-cause mortality				P value
	40-49 Y	50-59 Y	60-69 Y	70-79 Y	
DBP, mm Hg	87±3.6	87.5±4	86.8±3.9	87±4.2	0.873
SBP, mm Hg	133.4±8.8	133.2±8.9	136.6±8.1	140±10.5	0.022*
HDL, mmol/L	1.17±0.38	1.15±0.32	1.18±0.35	1±0.32	0.520
LDL, mmol/L	5.2±0.56	5.6±0.52	5.2±0.63	5.2±0.62	0.018*
TC, mmol/L	5.89±0.32	5.82±0.29	5.93±0.39	5.97±0.47	0.395
hs-CRP mg/L	1.82±1.2	2.59±1.6	2.55±1.9	2±1.4	0.275
CRP mg/L	1±0.45	0.74±0.45	0.9±0.62	0.81±0.4	0.231
BMI kg/m2	24.6±1.3	25.1±2.2	25.2±2.2	25±1.8	0.741
Uric Acid	5.6±2.1	5.9±1.7	5.8±1.6	6±2	0.928

* represents a significant difference at $P \leq 0.05$. Data are expressed as Mean±SD.

Regarding age groups, the results of SBP and LDL parameters showed a significant difference among all the studied age groups (p<0.005) for All-cause mortality patients, where p values are 0.022 and 0.018. However, there are no significant differences p>0.05 among all the studied age groups (p<0.005) for All-cause mortality patients in the other studied parameters.

Table 5: Distribution of the studied parameters values according to the age of CV mortality patients

Parameters	CV mortality				P value
	40-49 Y	50-59 Y	60-69 Y	70-79 Y	
DBP, mm Hg	86.2±4.2	85±3.1	86±3.3	85±3.2	0.492
SBP, mm Hg	137.3±8.3	139.8±8.6	140.9±7	141.5±8	0.461
HDL, mmol/L	1.18±0.3	1.37±0.32	1.1±0.28	1.37±0.34	0.002*
LDL, mmol/L	5.3±0.68	5.4±0.79	5.5±0.57	5.8±0.66	0.072
TC, mmol/L	5.6±0.6	6±0.4	6.13±0.7	6.16±0.8	0.138
hs-CRP mg/L	3.4±3.5	2±1.4	2.4±2.1	2.1±1.1	0.263
CRP mg/L	0.79±0.5	0.76±0.4	0.67±0.3	0.53±0.3	0.225
BMI kg/m2	25.8±3.7	27.3±3	26.8±2.9	26.3±2.1	0.472
Uric Acid	4.7±1.3	5.1±1.5	5.7±1.7	7±2	0.001*

* represents a significant difference at $P \leq 0.05$. Data are expressed as Mean±SD.

Regarding age groups, the results of HDL and Uric acid parameters showed a significant difference among all the studied age groups (p<0.005) for CV-cause mortality patients, where p values are 0.002 and 0.001. However, there are no significant differences p>0.05 among all the studied age groups (p<0.005) for CV-cause mortality patients in the other studied parameters.

Table 6: Frequency of patients according to gender

	Gender		
	Female	Male	
All-Cause Mortality	63 (46.67)	72 (53.33)	135 (57.4)
CV mortality	45 (45)	55 (55)	100 (42.6)
Total	108 (46)	127 (54)	235 (100)

This is no significant association between death frequency and gender groups, where the p-value is 0.895 (p>0.05). In addition, this is no significant difference in death frequency between male and female in both All-Cause Mortality and CV mortality cases, were *p*-value is 0.491 and 0.368 (p>0.05).

Table 7: Frequency of patients according to age

Type of death	Age roups				Total
	40-49 y	50-59 y	60-69 y	70-79 y	
All-Cause Mortality	17 (12.6)	37 (27.4)	59 (43.7)	22 (16.3)	135 (57.4)
CV mortality	11 (11)	22 (22)	43 (43)	24 (24)	100 (42.6)
Total	28 (11.9)	59 (25.1)	102 (43.4)	46 (19.6)	235 (100)

Regarding age frequency, this is no significant association between death frequency and age groups, where *p* value is 0.468 (p>0.05). This is a significant difference in death frequency among the age groups in both All-Cause Mortality and CV mortality cases, were *p* value is 0.000 and 0.000 (p<0.05).

In this study demonstrated elevated UA levels and were associated in both ACM and CVM women and men. The relationship between UA and hyperinsulinemia lead to reduce UA excretion in the kidney (Facchini, F., *et al.,* 1991) or indirectly during other influence on lipid profile (Matsuura, F., *et al.,* 1998) or metabolic syndrome such as HDL- cholesterol (Chen, L.Y., *et al.,* 2007). Possibility elevated UA be a marker of the kidney influence of insulin resistance and may lead to hyperinsulinemia (Krishnan, E., Pandya, B.J., *et al.,* 2012). Nevertheless, it has been suggested that UA may do weakness leptin-mediated simplification of insulin sensitivity and sympathetic increase activity and renal sodium excretion by rising proximal tubular sodium reabsorption. Leptin may so partially analyze the relationship between UA concentration and metabolic defect (Bedir, A. *et al.,* 2003).

Interestingly and according to figure 1 the highest rate mortality was in age 60-69 years in both ACM and CVM and the lowest rate of mortality in age 40-49 y in both categories.

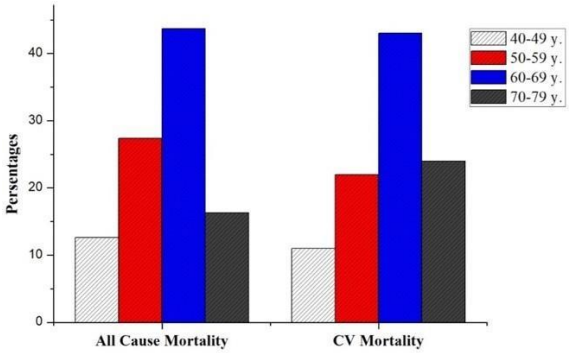

Figure 1: Cases distribution by Age groups

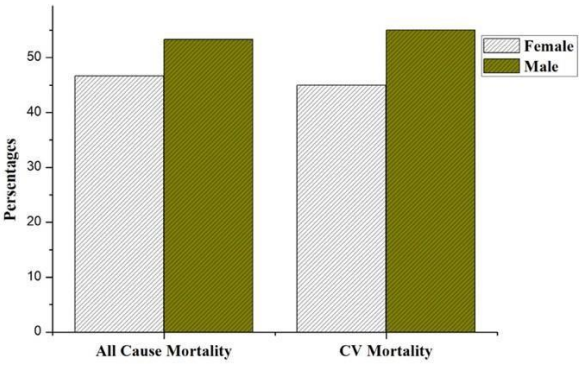

Figure 2: Cases distribution by Gender groups

In fig.2 in men was higher than women in mortality in both ACM and CVM. Since the 19 century high UA has been noted an associated with CVM (Davis, N.S., 1897) and after this date showed a lot of studies considered UA independent risk factor ACM andCVM (Okura, T. *et al.,* 2009 and Madsen, T.E., *et al.,* 2005). In this study included a large groups ACM and CVM were UA value more 7 mg/dl (Madsen, T.E. *et al.,* 2005). As well, an elevated UA level more than 7.5 mg/dl has been demonstrated to increase the risk CVM (Ndrepepa, G. *et al.,* 2012).In spite of many studies not considered UA independent risk factor mortality (Wheeler, J.G. *et al.,* 2005 and Kim, S.Y., *et al.,* 2010).In this investigation observed hyperuricemia in all risk factors mortality, but in CVM founded a significant difference in UA value while no significant differences in ACM.HUA related with gender women and men noted no significant difference in death frequency between male and female in both ACM and CVM found in previous studies (Nagahama, K. *et al.,* 2004 and Fang, J., *et al.,* 2000).

C-Reactive protein was a higher value in ACM than in CVM. In female mortality was higher compared with a male in the same category while in male CVM was higher relative female CVM and was more in ACM compare with CVM according to Table 1-3 respectively. Some research has been demonstrated CRP predict in dead non- CVD (Panero, F., Gruden, G., *et al.,* 2012), likewise observed elevated CRP in small age in Table 4 & 5. As mentioned in the previous studies (Lyngdoh, T., Marques-Vidal, P., *et al.,* 2011 and Ruggiero, C., *et al.,* 2006), elevated UA value until in the normal range, were also linked with an elevated in levels of inflammatory signs including CRP. UA may contribute effectively to the linked systemic inflammation in an integrated

manner to atherogenesis, as has been proven through studies in the laboratory (Lyngdoh, T. *et al.,* 2011 and Johnson, R.J., *et al.,* 2003). UA motivate inflammation by the output of pro-inflammatory mediators, including monocyte chemoattractant protein-1, interleukin-1β, interleukin-6, and tumour necrosis operator (Wang, R., Song, Y., *et al.,* 2016). Increase SUA is a marker elevated xanthine oxidase enzyme action, which behind produces of UA is involved in the production of reactive oxygen species (ROS), like superoxide through purine metabolism then perform in increased oxidative stress (Karantalis, V. *et al.,* 2013).

In an analysis total cholesterol (TC) and in table 3 increased in CVM more than ACM, also tend to rise in female more than male ACM reverse CVM that was higher in male than female therefore, TC has been associated with CVM in many recent studies (Liu, C.W., *et al.,* 2017) that predictive TC with CVM. The possible mechanism related to elevated UA to stopping hypertriglyceridemia is obscure. It has been predicted to be due to a rise Nicotinamide adenine dinucleotide phosphate (NADPH) requirement for anew fatty acid synthesis in fat men. With elevated NADPH, UA output is reinforced and this might increase serum UA levels (Vuorinen-Markkola, H. *et al.,* 1994). In this study, the relationship between SUA and blood pressure has been mentioned in many clinical studies

(Johnson, R.J. *et al.,* 2003, Fang, J., *et al.,* 2000, Conen, D., *et al.,* 2004 and Li, Y., *et al.,* 1997).

With a view to reach the target decreasing CVM into 20% and enhance cardiovascular health (CVH) by 20% in the year 2020, the American Heart Association (AHA) suggested the determination of perfect CVH depended on exemplary levels of seven of cardiovascular risk factors (CRFs) and health conducts (Lloyd-Jones, D.M. *et al.,* 2010). Regrettably, the prevalence of perfect CVH was only 0.1% in the United State (D. Mozaffarian, E., *et al.,* 2015). Low prevalence of AHA-described perfect cardiovascular health factors was also mentioned between civilian women and men in India (Gupta, B. *et al.,* 2017). Only 0.6% men and 2.6% women objects congregated all 7 health components (Wu, H.Y. *et al.,* 2013) and 26.9% offered with 5-7 perfect CVH metrics in the urban Chinese population (Zeng, Q. *et al.,* 2013). These outcomes detected that CRFs were not well controlled and enhance health side are needed to rise CVH.

In summary, these data had been found uric acid is increased in advanced age for each gender. This association a strong sign of serum uric acid to cardiovascular mortality and all-cause mortality. The mechanism increases uric acid that associated with risk factors are unknown. However, these data are considered in general favour that serum uric is a useful in the determination of risk factors, As well as work to find better treatments in the future to reduce the proportion of uric acid in patients with chronic diseases.

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Conflict of interest

Non.

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