ELECTRICAL CARDIOMETRY AND SERUMTHROMBOMODULIN FOR EVALUATION OF CARDIOVASCULAR RISK IN HAEMODIALYSIS CHILDREN

By

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Abstract

Background: *Pediatric haemodialysis cases have a high incidence of cardiovascular morbimortality. Endothelial dysfunction (ED) is present at early stages of chronic kidney disease (CKD). Electrical cardiometry (EC) has been recommended as a safe, accurate, and reproducible hemodynamic measurement technique in children and infants. Through the production of substances like nitric oxide (NO), prostacyclin, thrombomodulin (TM), and tissue plasminogen activator (TPA), they control vasodilatation, fibrinolysis, and thrombosis.* ***Objectives:*** *To evaluate whether EC can detect cardiac output (COP) in children undergoing haemodialysis and to assess whether thrombomodulin accurately reflects the cardiac dysfunction in those patients.* ***Methods:*** *This is a case-control observational study includes 45 children on regular haemodialysis admitted at haemodialysis unit and from outpatient clinic of Al-Zahraa University Hospital during the period from November 2021-December 2022 and 45 children with matched age and sex as controls. Moreover, 45 apparently healthy with matched age and sex-matched children were selected as a control group. We investigated the serum level of thrombomodulin by using Human Thrombomodulin ELISA Kits in addition to routine laboratory investigations* and *electrical cardiometry for assessment of some parameters of both groups.* ***Results:*** *There was a significant decrease in Hb level, platelets counts and TLC, while there was a significant increase in serum thrombomodulin levels in CKD patients on regular haemodialysis than the control group. Highly significant increase of electrical cardiometry regarding (HR, SV, CO, CI, TFC, ICON, VIC, PEP, STR) in CKD patients on regular haemodialysis than the control group*

Conclusion: *Children with CKD on regular haemodialysis have had a significant rise in the mean values of their cardiac markers and serum thrombomodulin level. There was a non-significant correlation between thrombomodulin serum level and electrical cardiometry.*

Keywords: Chronic kidney disease, Electrical Cardiometry, Thrombomodulin.

Introduction

The CKD in children contributes to the global health burden. It is defined as the presence of renal damage markers for at least three months along with signs of structural and functional kidney problems, in presence or absence of diminished glomerular filtration rate (GFR), which is manifested by pathologic changes or other markers of renal injury such as blood, urine abnormalities or in radiological tests abnormalities; or GFR <60mL/min/1.73 m2 for three months or more, with or without renal injury **(Becherucci et al., 2016; Uwaezuoke et al., 2018)**. It has been demonstrated that pediatric haemodialysis patients are more susceptible to cardiovascular morbimortality **(Querfeld and Schaefer, 2020)**. Endothelial dysfunction (ED) is thought to be present in the initial stages of CKD **(Drożdż et al., 2016)**. As CKD progresses, there is a corresponding increase in the excess risk of cardiovascular death for patients with ED. In fact, the risk excess for this outcome is fourty percent in cases with a GFR between 45 and 59 mL/min/1.73 m^2, and 340% in cases with ESKD (GFR < 15mL/min/1.73m^2) **(Roumeliotis et al., 2020)**. In order to keep the circulatory system balanced, endothelial cells are essential. Through the production of substances like NO, prostacyclin, TM, and TPA, they control vasodilatation, fibrinolysis, and thrombosis **(Neubauer and Zieger, 2022)**. Reduced protective substance release is caused by endothelial damage, whereas increased counteractive substance release—including endothelium I, angiotensin II, plasminogen activator vasoconstriction, platelet activation, and pro-thrombotic and anti-fibrinolytic activity—is also a result **(Dane et al., 2018)**.

The transmembrane glycoprotein thrombomodulin (TM) has five domains. The binding of thrombin and stimulation of protein C are the mechanisms through which it has an anticoagulant effect. Through the deactivation of tissue plasminogen activator inhibitor and the degradation of active factors V and VIII, active protein C suppresses the coagulation cascade **(Yamakawa et al., 2019)** Additionally, thrombomodulin has anti-inflammatory properties. Endothelial cell injury causes the transmembrane part to be released, known as a soluble TM (s TM), and the TM molecule loses its ability to provide vasoprotection **(Krzanowski et al., 2017)**.

Electrical cardiometry (EC) has been suggested as a method for measuring children's and infants' hemodynamics that is secure, precise, and repeatable **(Narula et al., 2017)**. EC could be used as a valid indicator in terms of COP monitoring in several conditions, such as cases of critical illness, operative contexts, cardiac catheterizations, and in children with congenital heart diseases (CHD) **(Sumbel et al., 2022)**

Ethical consideration:

1. An informed oral and written was obtained from all parents of both patients and control groups before getting them involved in the study.
2. The researcher explained the stages, the aims, the potential benefits and hazards of the study to all parents of the patients and control groups.
3. The patients had the right to leave the study at any time.
4. Confidentially and privacy were respected.
5. Ethical approval was obtained from the ethics committee of the Pediatrics department at the faculty of medicine for girls at Al-Azhar University.
6. No conflicts of interest are to be declared, as reported by the authors.
7. FINANCIAL DISCLOSURE / FUNDING:

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Inclusion criteria:

1. Age ranges from 4 to 18 years.
2. Children with CKD on regular haemodialysis more than 3 months.

Exclusion criteria:

A. Children with primary cardiac diseases (CHD, Rheumatic heart disease, Cardiomyopathy) will be excluded from the study

B. Other chronic illness.

Sample size calculation

The sample size calculation was done by MedCalc Software Ltd v. 20 with 80% power, 5% confidence limit, correlation coefficient between thrombomodulin level and left ventricular mass index (LVMI) was 0.293 according to a previous study **(Drożdż et al., 2018)**. One case was added to overcome dropout. Therefore, 90 patients were recruited in the study.

Study procedure:

This study is a case-control observational study was carried out during the period from November 2021 to December2022 at the nephrology unit of AL-Zahra University Hospital, Al-Azhar University in Egypt on 45 children with ESRD on regular haemodialysis for 4 hours/setting, 3 times weekly with low flux polysulphne dialyzer, in addition, 45 matched age and sex healthy children as a control group.

The principal goal was to evaluate whether electrical cardiometry can detect cardiac output in children undergoing haemodialysis and to assess whether thrombomodulin accurately reflects the cardiac dysfunction in those patients.

Method:

All included patients were subjected to;

1- Full medical history taking including:

Cause of CKD, duration of both kidney impairment & haemodialysis and history of any other diseases.

2- Thorough clinical examination: General and Systemic.

- **General examination** including (weight, height, blood pressure), manifestations of volume status (congested neck veins, puffy eyes, lower limb edema, respiratory distress, sunken eyes).
- **Systemic examination** with particular emphasis on cardiac examination.

3- Lab. evaluation including:

A. Complete blood picture**,** serum calcium, serum phosphate, serum urea**,** serum creatinine**,** serum cholesterol and serum iron and ferritin.

B. Specific investigations including:

1- Estimation of serum thrombomodulin by using human thrombomodulin ELISA Kits.

Two ml of venous blood was withdrawn from each participant; then the blood was left to clot and serum was separated. The serum was allowed to clot for 15 min at 22 °C. The sample was centrifuged at 2000–3000 RPM for 20 min after cautious labeling until the time of the assay of thrombomodulin by using the Human Thrombomodulin ELISA Kit, USA.

2- Electrical cardiometry for assessment of the following parameters including: heart Rate (HR), stroke volume (SV), SV index (SVI), COP, cardiac index (CI), thoracic fluid content (TFC), index of contractility (ICON), SV variation (SVV), variation of icon (VIC), pre-ejection period (PEP), left ventricular ejection time (LVET), systolic time ration (STR).

Statistical Analysis

Data were collected, revised, coded and entered to the SPSS, IBM version 20. The $\chi 2$ test was used to compare between two groups with qualitative data were done by using Chi-square test and/or Fisher exact test was used when the expected count in any cell was less than 5. Student's test was used to compare between two independent groups with quantitative data were done by using independent t-test when the data were parametric and Mann-Whitney test when the data were non-parametric. The CI was set to 95% and the margin of error accepted was set to 5%. Thus, the p-value was considered significant when $P < 0.05$.

Results:

Table 1. Descriptive data of patient's group regarding age, sex.

Variable		**Patients group**
		No.= 45
Age (years)	Mean ±SD	11.42 ± 3.01
Sex	Female	12 (26.7%)
	Male	33 (73.3%)

This table shows age and sex distribution in patient's group.

Table 2. Laboratory data and serum electrolytes in patient's group.

Variable		Patients group
		No.= 45
CBC		
Heamoglobin (Hb) (gm/dl)	Mean ±SD	10.11 ± 2.35
Mean corpuscular volume (MCV) (fL)	Mean ±SD	84.84 ± 6.55
Platelets (PLT) (µL)	Mean ±SD	230.58 ± 75.10
Total leucocyte count (TLC) (µL)	Mean ±SD	6.61 ± 1.83
eGFR (ml/min/1.73m^2)	Median (IQR)	8.3 (6.2 − 11.2)
Serum electrolytes		
Serum urea (mg/dl)	Mean ±SD	186.29 ± 222.34
Serum Na (mmol/l)	Mean ±SD	139.73 ± 4.77
Serum K (mmol/l)	Mean ±SD	5.55 ± 1.24
Serum Creat (mg/dl)	Mean ±SD	8.12 ± 2.52

SD: standard deviation; IQR: Interquartile range

This table shows there were significant reductions in Hb level, platelet count and total WBC count in patients' group compared to the controls. There was significant disturbance in serum electrolytes in patients' group.

Table 3. Etiology of CKD among the study patients.

Etiology of chronic kidney disease	Total no. = 45
Hereditary	**13 (28.9%)**
AR PCK, congenital hepatic fibrosis	1 (2.2%)
Barder-Bield syndrome	2 (4.4%)
Bartter syndrome	3 (6.7%)

Jubert syndrome	2 (4.4%)
Nephronophthisis	2 (4.4%)
Polycystic kidney disease	3 (6.7%)
Acquired	**14 (31.1%)**
Atypical nephrotic syndrome	1 (2.2%)
Grade 2 nephropathy	1 (2.2%)
Chronic interstitial nephritis	3 (6.7%)
Focal segmental glomerulosclerosis	5 (11.1%)
Hemolytic uremic syndrome	1 (2.2%)
Lupus nephritis (LN)	1 (2.2%)
Mesengial Proliferative Glomerulonephritis	1 (2.2%)
Obstructive uropathy	1 (2.2%)
Congenital	**8 (17.8%)**
Bilateral vesico ureteric reflux	2 (4.4%)
Posterior urethral valve	2 (4.4%)
Vesico ureteric reflux	4 (8.9%)
Neurogenic bladder	1 (2.2%)
Unknown	**10 (22.2%)**
Bilateral atrophic kidney	9 (20.0%)
Thrombotic micro angiopathy	1 (2.2%)

This table shows that the most common cause of CKD in the dialysis group is acquired cause in 14 (31.1%) patients followed by hereditary cause in 13 (28.9%) patients, then unknown in 10 (22.2%) ended congenitally in 8 (17.8%).

Table 4. Comparison between patients' group and control group regarding age, sex, anthropometric measurements, blood pressure, consanguinity and family history.

Variable		**Patients' group**	**Control group**	**Test value**	**P- value**	**Sig.**
		No.= 45	**No.= 45**			
Age (years)	Mean ±SD	11.42 ± 3.01	10.64 ± 3.32	1.164	0.247	NS

Sex	Female	12 (26.7%)	20 (44.4%)	3.103*	0.078	NS
	Male	33 (73.3%)	25 (55.6%)			
Weight (Kg)	Mean ±SD	28.61 ± 10.12	35.42 ± 10.84	-3.081•	0.003	HS
Consanguinity	-ve	21 (46.7%)	39 (86.7%)	16.200*	0.000	HS
	+ve	24 (53.3%)	6 (13.3%)			
Family history of CKD	No	30 (66.7%)	44 (97.8%)	14.899*	0.000	HS
	Yes	15 (33.3%)	1 (2.2%)			
Weight z-score	Median (IQR)	-0.46 (-1 – 0.27)	0.27 (-0.46 – 0.91)	-3.016≠	0.003	HS
Height (cm)	Mean ±SD	121.82 ± 17.40	137.44 ± 17.52	-4.244•	0.000	HS
Height z-score	Median (IQR)	-0.51 (-1.03 – 0.28)	0.54 (-0.24 – 1.23)	-3.930≠	0.000	HS
BMI (kg/m^2)	Mean ±SD	19.13 ± 3.81	18.54 ± 2.76	0.845•	0.400	NS
BMI z-score	Median (IQR)	-0.07 (-0.76 – 0.44)	-0.22 (-0.67 – 0.38)	-0.379≠	0.704	NS
Systolic B.P (mmHg)	Mean ±SD	124.89 ± 21.70	110.22 ± 8.39	4.228•	0.000	HS
Diastolic B.P (mmHg)	Mean ±SD	82.56 ± 15.62	70.22 ± 6.90	4.845•	0.000	HS

IQR: Interquartile range; *: Chi-square test P > 0.05: NS P < 0.05: S P < 0.01: HS

This table demonstrates that there was no significant difference between patient's group and control group regarding age and sex. While, highly significant decrease in the z-score of the anthropometric measurements in patients' group in comparison with the controls, also there was highly significant increase in systolic blood pressure and diastolic blood pressure in patients' group compared to the controls. In addition, there was a highly significant difference in consanguinity and family history in patients' group compared to the controls.

Table 5. Comparison between patient's group and controls group regarding CBC parameters and serum thrombomodulin.

		patient group	Control group	Test value•	P- value	Sig.
		No.= 45	No.= 45			
Hb (g/dl)	Mean ±SD	10.11 ± 2.35	11.81 ± 0.75	-4.629	0.000	HS
MCV (fL)	Mean ±SD	84.84 ± 6.55	74.61 ± 4.47	8.646	0.000	HS
PLT (µL)	Mean ±SD	230.58 ± 75.10	266.02 ± 50.56	-2.626	0.010	S
TLC (µL)	Mean ±SD	6.61 ± 1.83	9.51 ± 1.82	-7.545	0.000	HS
Serum Thrombomodulin (ng/ml)	Median (IQR)	2.73 (2.25 – 7.23)	1.88 (1.47 – 3.21)	-3.938≠	0.000	HS

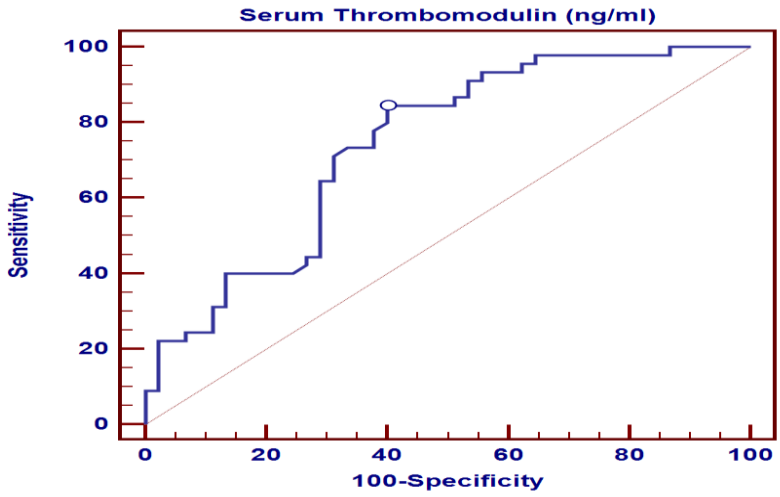
Chi-square test P > 0.05: NS P < 0.05: S P < 0.01: HS ≠: Mann-Whitney test *: IQR: Interquartile range

This table shows that there was a highly significant decrease in Hb level, platelet count and TLC and increase in MCV in patients' group compared to the controls. Additionally, a highly significant increase in serum thrombomodulin in patient's group compared to the controls was observed.

Table 6. Correlation between serum thrombomodulin and the study clinical & laboratory parameters in patient's group.

	Serum Thrombomodulin (ng/ml)	
	R	**P-value**
Age	-0.006	0.967
WT	0.035	0.819
Weight z-score	**-0.196**	**0.065**
HT	0.134	0.381
Height z-score	**-0.167**	**0.116**
BMI	-0.231	0.127
BMI z-score	**-0.196**	**0.064**
Systolic	0.011	0.942
Diastolic	-0.027	0.861
Hb	-0.088	0.567
MCV	-0.150	0.325
PLT	0.103	0.502
TLC	-0.090	0.555
Serum urea	-0.080	0.600
Serum Na	0.100	0.514
Serum K	-0.186	0.222
Serum cereat	-0.117	0.443
Serum Albumin	-0.374*	0.011
Serum Ca	-0.200	0.187
Serum phosphorus	0.190	0.211
Serum para thyroid H	-0.097	0.528
Serum ferritin	-0.155	0.311

This table shows there was non-significant correlation between serum thrombomodulin and (age, weight, BMI, systolic blood pressure (SBP) and diastolic blood pressure (DBP)). Additionally, there was a significant negative correlation between serum thrombomodulin and serum albumin, while non-significant correlation with other study laboratory parameters was observed.



Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
>2.02	0.741	84.44	60.00	67.9	79.4

The ROC curve of serum thrombomodulin with cut off value the sensitivity and the specificity are 84.44% and 60.00% to predict CKD.

Table 7. Comparison between patients' group and control group regarding electrical cardiometry.

Electrical cardiometry	patients' group	Control group	Test value•	P-value	Sig.

		No.= 45	No.= 45			
HR	Mean ±SD	106.78 ± 18.82	78.62 ± 15.16	7.816	0.000	HS
SV	Mean ±SD	46.02 ± 19.42	35.73 ± 2.17	3.533	0.001	HS
CO	Mean ±SD	4.79 ± 1.59	3.33 ± 0.83	5.448	0.000	HS
CI	Mean ±SD	5.30 ± 1.27	3.04 ± 0.61	10.720	0.000	HS
TFC	Mean ±SD	41.80 ± 12.38	28.62 ± 3.49	6.871	0.000	HS
ICON	Mean ±SD	97.49 ± 32.61	52.33 ± 9.08	8.951	0.000	HS
SVV	Mean ±SD	15.44 ± 6.57	8.60 ± 2.76	6.441	0.000	HS
VIC	Mean ±SD	23.82 ± 10.46	11.07 ± 5.20	7.327	0.000	HS
PEP	Mean ±SD	102.18 ± 21.63	86.64 ± 14.77	3.978	0.000	HS
LVET	Mean ±SD	243.53 ± 36.21	233.98 ± 21.82	1.516	0.133	NS
STR	Mean ±SD	0.44 ± 0.11	0.36 ± 0.05	4.407	0.000	HS

P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

This table shows a highly significant increase of electrical cardiometry according to (HR, SV, CO, CI, TFC, ICON, VIC, PEP, STR) regarding patients' group and control group.

Table 8. Correlation for serum thrombomodulin with electrical cardiometry regarding patient group and control group.

	Serum Thrombomodulin (ng/ml)	
	R	P-value
HR	-0.014	0.927
SV	0.166	0.276
CO	0.219	0.148
CI	0.251	0.096
TFC	0.047	0.761
ICON	-0.148	0.333
SVV	0.007	0.963
VIC	0.281	0.061
PEP	0.221	0.144
LVET	-0.034	0.822
STR	-0.027	0.863

This table shows non-significant correlation between serum thrombomodulin and electrical cardiometry

Discussion

According to the current data, there are more male patients receiving haemodialysis (73.3%) than female patients (26.7%). According to **Harambat et al. (2018)**, there was a female predominance (the male to female ratio was 1.3/2.0). Furthermore, the current study's findings concurred with those of **Becherucci et al. (2016)**, who showed that while congenital aberrations of the kidney and urinary tract are more common in males than in females.

In this study, highly statistically significant increases in SBP and DBP were detected in the patient's group compared to the control group (P value<0.001). This came in agreement with **Haskin et al. (2015)** and **Masalskienė et al. (2021)**; who revealed that the dialysis patients were significantly had higher blood pressure values than the control group. This may be caused by additional risk factors appear in dialyzed cases which include (fluid overload, inappropriate high renin–angiotensin system, sympathetic over activity, etc.) **(Flynn, 2019)**.

Our study revealed that there was highly statistically significant increase in positive consanguinity and family history among patients' group compared with the control group (P<0.001). Similarly, **Ory et al. (2018)** and **Al Riyami et al. (2019)** in Saudi Arabia and Omani, respectively, and recorded that consanguinity was noticed in 28% and 41.8% of the patients, respectively, and 28.6% and 31.3% of them had a positive family history of renal disease.

Our findings showed that CKD patients were anemic with significant reduction in Hb level and Hct % in cases than the controls (p <0.001). This came in accordance with **Abdel Kereem et al. (2022)**, who found that the mean hemoglobin level was significantly lower in pre-dialysis and dialysis groups as compared to that of control group, their explanation was, those patients have a high level of serum hepcidin is accompanied by a decrease in absorption of iron.

In our study, the most frequent cause of CKD was acquired causes (31.1%) followed by hereditary causes, congenital causes (17.8%) and unknown causes (22.2%). Likewise, **Mohammed et al. (2013)** recorded that acquired causes is the most frequent cause of CKD in developing countries. In disagreement, in Egypt, **Safouh et al. (2015)** and **Kaspar et al. (2016)**, revealed that congenital urological malformation comprised 46% of the underlying etiology in their patients. The difference in the studies regarding to the etiology of CKD may attributed to sample size.

The present study demonstrated that there was significant elevation in serum thrombomodulin level in dialysis group compared to controls ($p < 0.01$). This may be explained by ED or low-grade immune-mediated inflammation among CKD patients **(Roumeliotis et al., 2020)**. According to **Yu et al. (2021)**, CKD patients had greater serum thrombomodulin levels than healthy individuals, which is consistent with our findings. Furthermore, our findings supported those of **Drożdż et al. (2018)**, who found that

TM levels increased with CKD stage (stages 1+2, 3, and 4, respectively) and that there were significant differences in median TM level between CKD stages.

The present study revealed that non-significant correlation between serum thrombomodulin and the study clinical parameters. These findings concurred with those of **Krzanowski et al. (2017)**, who discovered that there was no correlation between thrombomodulin concentrations and clinical parameters or age. This suggests that thrombomodulin may be a determinant of progressive calcification and vascular injury in individuals with compromised renal function.

In the present study, serum thrombomodulin showed non-significant correlation with laboratory parameters except serum albumin there was a significant negative association between serum thrombomodulin (P value=0.01). These outcomes were in the same line with **Dong et al. (2014)**, who found that the transcapillary escape of macromolecules that enhance atherosclerosis, such as albumin and lipoproteins, combined with changes in levels of Von Will brand factor, fibrinogen, TM, and PAI, is believed to increase CVD.

On the other hand, we disagreed with those of **Drożdż et al. (2018)**, who found a strong positive correlation between thrombomodulin concentrations and higher albuminuria. However, they also demonstrated a strong positive association between TM concentrations and urea & creatinine, which was the opposite of the present findings.

In the present study, ROC curve of serum thrombomodulin with cut off value revealed that the sensitivity and the specificity were 84.4% and 60% to predict CVD in CKD patients. In the same line with our results, **Yu et al. (2021)** reported that ROC analysis demonstrated that serum TM level discriminated cases with active LN from healthy individuals with sensitivity and specificity rates of 100% for both (P<0.001).

Based on the outcomes of the current investigation, there was a highly statistically significant increase in the mean values of HR, SV, CO, CI, TFC, ICON, VIC, PEP and STR among patients' group in comparison with the control group (P <0.001). These findings concurred with those of **Wilken et al. (2020)**, who found that EV detected substantial alterations in cardiovascular parameters related to pediatric HD patients. Similarly, **Amoozgar et al. (2018)** recorded a significant drop in left ventricular systolic and diastolic dimensions and volume (P<0.001) in children with ESRD being on long-term haemodialysis. Finally, the present study demonstrated non-significant correlation between serum thrombomodulin and electrical cardiometry parameters among patient group (P >0.05).

Conclusion:

Significant rise in serum thrombomodulin level and cardiac markers was observed in children with CKD on regular haemodialysis with non-significant correlation between serum thrombomodulin level and electrical cardiometry parameters.

Recommendations:

Early and regular echocardiographic evaluation should be planned as a part of the management protocol of uremic children to detect early cardiac changes. Assessment of thrombomodulin in CKD patients in a wide scale in order to study its role in renal and cardiovascular risks.

Limitations:

The small sample size, short duration, and being a single-center (one hospital) study.

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