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# Abnormal inpatient EEG predicts seizure occurrence independently of renal function



Christian Matta<sup>a</sup>, Rouba Hamze<sup>b</sup>, Rachelle Abi-Nahed<sup>a</sup>, Hiba Azar<sup>c</sup>, Karine J. Abou Khaled<sup>a,\*</sup>

<sup>a</sup> Department of Neurology, Hotel-Dieu de France Hospital, Saint-Joseph University, Beirut, Lebanon

<sup>b</sup> Department of Medicine, Hotel-Dieu de France Hospital, Saint-Joseph University, Beirut, Lebanon

<sup>c</sup> Department of Nephrology, Hotel-Dieu de France Hospital, Saint-Joseph University, Beirut, Lebanon

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Keywords: EEG Seizure Renal function	<ul> <li>Purpose: The study aimed to determine prospectively whether there is a significant relationship between renal function as per the estimated glomerular filtration rate (eGFR), and the occurrence of seizures in patients who have no history of epilepsy and who required an EEG while hospitalized.</li> <li>Methods: Adult patients who were hospitalized at Hôtel-Dieu de France University Hospital in Beirut and who required routine EEGs were included over a period of 13 months. We excluded critical patients or those with history of epilepsy.</li> <li>Data was analyzed depending on the EEG result and according to the baseline eGFR estimated by the CKD-EPI formula. Patients were followed prospectively by phone interview at 6 months for occurrence of seizure or death. Results: Sixty one patients with a mean age of 66 (age range 19 to 95) were included (52 % were females). Of the 23 patients who had normal EEGs, 43.47% had abnormal eGFR, and none of them had a seizure. Of the patients with abnormal EEGs, 71.05% had abnormal eGFR, of which 7 had seizures. A significant relationship was found between having an abnormal EEG is normal, there will be lower risk to develop a seizure at 6 months. Conclusions: While eGFR and the incidence of seizures were not directly related, our study showed that patients with abnormal EEG were more likely to develop seizures regardless of their baseline eGFR.</li> </ul>

## Introduction

Routine inpatient electroencephalography (EEG) is commonly used as a diagnostic tool in the care of patients admitted for various medical conditions. Its diagnostic yield and usefulness in general noncritical patients have been investigated [1] but its potential to predict seizures in certain groups of patients, such as those with altered renal function, is not clear [2]. Patients with renal insufficiency seem to have a lower seizure threshold in settings of hemodynamic instability, electrolyte disorders, or hemodialysis [3]. In fact, seizures in these patients are due to multiple factors including the accumulation of uremic toxins, electrolyte or glucose disturbances, sepsis, stroke, certain drugs, subdural hematoma, and posterior reversible encephalopathy syndrome [4]. Although rapid rises in blood urea nitrogen (BUN) may be a strong seizure trigger, other metabolic abnormalities can be implicated and absolute BUN levels are not a reliable indicator of seizure risk [3,5,6]. There is some evidence that seizures occur in 2 to 15 % of patients with renal failure or on hemodialysis [5,7–11] but there's no clear evidence whether having an abnormal renal function could predispose to developing future seizures, which prompted us to plan the current study. Our aim was to determine prospectively whether there is a significant relationship between renal function as per the estimated glomerular filtration rate (eGFR), and the occurrence of seizures in patients who have no history of epilepsy and who required an EEG during their hospital stay.

Our main objectives were to study the risk of developing seizures at 6 months in these patients according to eGFR and baseline inpatient EEG result.

Sepsis and carbapenem use are well known factors for altered mental status and cerebral dysfunction at short and long terms [12–15]. Therefore, in our work, we studied whether these factors affected the occurrence of seizure at 6 months in the presence or absence of renal

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<sup>\*</sup> Corresponding author at: Saint Joseph University, Hotel-Dieu de France Hospital, Blvd Alfred Naccache, Achrafieh, Beirut, Lebanon. *E-mail address:* karine.aboukhaled@usj.edu.lb (K.J. Abou Khaled).

impairment.

## Methods

This is an observational analytical cohort study.

#### Patients population

Our population included patients who were hospitalized at Hôtel-Dieu de France University Hospital in Beirut, a tertiary care center affiliated to the Faculty of Medicine of Saint-Joseph University. All hospitalized patients aged 18 and above who required an EEG, regardless of its indication were considered. We excluded patients with history of epilepsy or any previous seizure, acute renal failure, and those in critical condition (requiring mechanical ventilation, vasopressors, septic shock) or with life expectancy of less than 6 months.

Patient recruitment was done over a total of 13 months, following approval by the institution ethics committee. Written and informed consent was obtained directly from the participants or their primary caregiver.

# Data collection

Patients' medical records were reviewed for demographical and clinical data collection. The most relevant information obtained included: age, sex, reason for admission, medications, medical and surgical history, brain imaging. The biological markers noted were plasma creatinine (micromol/L), serum sodium (in mEq/l), serum magnesium (in mEq/l), serum calcium (in mmol/l), and urea (in mmol/ 1). Whenever the patient had several blood tests, the one done on the day of the EEG was considered and retained for analysis. We used the CKD-EPI formula (The Chronic Kidney Disease-Epidemiology collaboration) to estimate the glomerular filtration rate. Stage 1 corresponds to normal eGFR above 90 ml/min. In stage 2, there is a slightly reduced eGFR of 60 to 89 ml/min. Stage 3 occurs when eGFR falls between 30 and 59 ml/min). In stage 4 the eGFR is 15 to 29 ml/min, and in stage 5 it's below 15 ml/min [16,17]. The EEGs were all "routine EEGs" with an average duration of 20-30 min using 19 electrodes EEG cap. They were all uniformly performed on a Nicolet/ Natus EEG-system under the same conditions in the neurophysiological laboratory of Hôtel-Dieu de France

Hospital [18]. An example is shown in Fig. 1.

The subjects were divided into two groups based on their EEG result: normal v/s abnormal. Subsequently the EEG abnormalities were classified as such: EEG slowing (focal or diffuse, mild, moderate, or severe), sporadic epileptiform discharges (SD), triphasic waves and seizures [19]. Background slowing was graded as the following [20,21]:

a-Mild: Slowing of the background rhythm, especially of the theta type.

b-Moderate: an intermittent appearance of delta waves on a slowed background rhythm.

c-Severe: delta activity occupying more than 80% of the background. Then, each of the two groups was divided into two subgroups according to eGFR: a group with normal kidney function (control group) and another one with decreased kidney function. The main endpoints were the occurrence or not of a seizure within the 6 months following the performance of the EEG.

#### Follow-up

The follow-up of the patients was done remotely 6 months after completion of the inpatient EEG through a telephone interview done by one of the physicians (CM, RH). Specific questions were asked looking at the possible occurrence of a generalized or focal onset seizure, or death [22] (cf supplementary file).

## Statistical analysis

Statistical analysis was done using SPSS version 23 software. Descriptive tests of the type of mean, frequency, median and percentage were used for the biological parameters.

Chi-square test was used to compare the risk of developing epileptic seizures in patients with an abnormal EEG according to the different types of EEG abnormalities found. Fisher test was used to test the hypothesis whether patients with renal insufficiency are at higher risk of having an abnormal EEG and/or developing an epileptic seizure in the future. It was also used to test whether sepsis and the use of specific antibiotics (mostly carbapenems) was associated with higher risk of seizure occurrence or death at 6 months.

The results were considered statistically significant for a p value < 0.05.



Fig. 1. EEG example using bipolar montage in an 83-year-old woman known to have hypertension and dyslipidemia, admitted for urinary tract infection and somnolence. Her Brain MRI showed bilateral white matter changes. EEG revealed intermittent diffuse delta and theta slowing maximal over the fronto-temporal regions.

Lastly, to understand the impact of each variable on the final outcome, we applied logistic regression analysis, which enabled us to explore the relationship and potential effects of the predictors on the dependent variable.

## Results

## Patients' characteristics and baseline laboratory and EEG findings

Over a period of 13 months, a total of 61 patients (52.5% females) were recruited for the study with a mean age of 66 [age range 19 to 95] (Table 1). Approximately 74% of patients had at least one cardiovascular risk factor (such as high blood pressure or dyslipidemia), 7% had a serious heart disease (history of coronary heart disease, heart failure) and 9% had a history of cancer.

Impaired consciousness and behavioral disorders were the main reasons for admission (44.3% of the cases), followed by stroke (27%), gait disorders (10%) and fever (8%).

In 78% of cases, brain imaging was normal. Eleven patients (18%) had small vessel disease.

Carbapenems were prescribed in 14.8% of the patients and 18% of patients developed sepsis during hospital stay.

Regarding renal function, mean eGFR was 76.1 ml/min/1.73 m2 and CKD stages distribution was as represented in Table 2.

Overall, 23 patients had a normal EEG (37.4%), and 38 patients (62.3%) had abnormalities such as in Fig. 1 and were classified as:

- Diffuse slowing, subdivided into mild (19.7%), moderate (27.9%) or severe (4.9%).
- Focal slowing (8.2%).
- Sporadic epileptiform discharges (1.6%).

# Outcome at 6 months

A phone interview was conducted 6 months after the initial EEG. During this time interval, 7 subjects (11.5%) developed seizures, including 2 with myoclonic jerks, 3 with tonic-clonic seizures and 2 with focal seizures. Table 3 summarizes the characteristics of patients with and without seizures.

None of the patients who had normal EEG developed a seizure within 6 months following completion of the EEG v/s 18.4% from the ones who had abnormal EEG at baseline. Of note, 3 out of 11 patients with small

Focal slowing

Epileptiform discharges

# Table 1

Cha

haracteristics of patients.							
		Ν	(%)	95.0%	CI	Mean	SD
Age (years)						65.951	21.084
Sex	М	29	47.5%	35.4%	59.9%		
	F	32	52.5%	40.1%	64.6%		
eGFR CKD-EPI category	eGFR CKD-EPI $\leq 30 \text{ ml/min/m}^2$	10	16.4%	8.8%	27.1%		
	$30 < eGFR CKD-EPI <= 60 ml/min/m^2$	7	11.5%	5.3%	21.2%		
	eGFR CKD-EPI > 60 ml/min/m <sup>2</sup>	44	72.1%	60.0%	82.2%		
eGFR CKD-EPI						76.090	35.419
Na (mEq/l)						138.311	4.422
Mg (mEq/l)						0.808	0.104
Ca (mmol/l)						2.264	0.188
Urea (mmol/l)						9.946	8.558
Sepsis		11	18.0%	10.0%	29%		
Carbapenem exposure		9	14.8%	7.6%	25.2%		
EEG findings	Normal background	23	37.7%	26.3%	50.2%		
	Mild slowing	12	19.7%	11.2%	30.9%		
	Moderate slowing	17	27.9%	17.8%	40.0%		
	Severe slowing	3	4.9%	1.4%	12.5%		

Ca: calcium (Normal range: 2.1 to 2.6 mmol/l), CI: confidence interval, SD: Standard deviation, EEG: electroencephalogram, eGFR CKD-EPI: Estimated Glomerular Filtration Rate using the chronic kidney disease (CKD)-Epidemiology Collaboration (EPI) equation, F: female, M: male, Mg: magnesium (abnormal value less than 0.7 mmol/l), Na: Sodium (Normal range: 135 to 145 mmol/l), and abnormal value of urea level greater than 7 mmol/l.

8 2%

1.6%

3.2%

0.2%

5

1

Table 2

one stages ansansans	CKD	stages	distri	bu	tio	n
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CKD stages	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Number	24	20	7	4	6
(%)	(39.34%)	(32.78%)	(11.4%)	(06.55%)	(09.83%)

## Table 3

Characteristics of patients with and without seizures.

		Seizure + (N)	Seizure – (N)
Sex	М	2	27
	F	5	27
eGFR CKD-EPI <= 3	0 ml/min/m <sup>2</sup>	1	9
30 < eGFR CKD-EPI	$<= 60 \text{ ml/min/m}^2$	1	6
eGFR CKD-EPI > 60	ml/min/m <sup>2</sup>	5	39
EEG findings	Normal background	0	23
	Mild slowing	2	10
	Moderate slowing	3	14
	Severe slowing	1	2
	Focal slowing	0	5
	Epileptiform discharges	1	0
Sepsis		0	11
Carbapenem exposu	re	1	8

EEG: electroencephalogram, eGFR CKD-EPI: Estimated Glomerular Filtration Rate using the chronic kidney disease (CKD)-Epidemiology Collaboration (EPI) equation, F: female, M: male, Seizure:(+) for present and (-) for absent.

vessel disease on brain MRI had a seizure within that time frame but that was statistically not significant (p value of 0.069).

Regarding specific antibiotic use, we noted that among patients treated with carbapenems, 33% died and 11.1% had seizures during the follow up period of 6 months, whereas none of the patients with diagnosed sepsis developed any seizures. Moreover, there was a trend towards an increased risk of death within the 6 months following discharge from hospital in patients treated with carbapenems (p = 0.059).

Death occurred in 7 patients (11.5%) and 5 of these 7 patients had abnormalities on the initial EEG.

Association of EEG and eGFR (Results are summarized in Table 4).

A total of 37 patients had an abnormal eGFR. Of these 73% had EEG abnormalities and a total of five had experienced seizures at 6 months follow-up (13.5%).

Among patients with an abnormal EEG, 71.05% had an eGFR of less

17.0%

7.4%

#### Table 4

Association of EEG and eGFR.

		EEG Normal N	Abnormal N
eGFR	>90	13	11
	<90	10	27*

EEG: electroencephalogram, eGFR: Estimated Glomerular Filtration.

\* Low eGFR (<90 ml/min/1.73 m2) was associated with increasing risk of having EEG abnormalities with a statistically significant p-value (p = 0.03).

than 90. Low eGFR was significantly associated with abnormalities on EEG (p value =  $0.03^{*}$ ).

Of the 27 subjects with low eGFR, 24 had generalized slowing on EEG, while 3 had focal slowing. None of them had sporadic epileptiform discharges.

# Correlations between EEG result and risk of developing seizures at 6 months depending on the renal function:

A significant relationship was found between having an abnormal EEG and the risk of developing an epileptic seizure in the future (p-value = 0.038). In hospitalized patients, independently of eGFR, an abnormal EEG predicted the occurrence of a seizure within 6 months period. Using logistic regression, renal function was not an independent predictor of seizures at 6 months post discharge (p-value = 1). Studying interactions between variables, tests showed that there was no interaction between eGFR and urea nor between eGFR and EEG and hence no effect of the interaction of these variables on the occurrence of seizure in that time interval.

Whatever the eGFR is, if the baseline EEG is normal, there will be lower risk of developing a seizure at 6 months (negative predicting value of 100%) with a specificity of 42.6%.

On the other hand, if the baseline EEG is abnormal, 18.4% will have a seizure at 6 months with a sensitivity of 100 % (Table 5).

## Discussion

There is a growing interest exploring biological or electrographic biomarkers to predict the risk of developing seizures in people with medical conditions or elderly patients. That was our objective. We designed our study to assess the relationship between routine EEG findings, renal function and occurrence of seizures in the future.

In hospitalized patients, and regardless of EEG findings we found that eGFR did not prove to be a significant risk factor for having a seizure in the following 6 months, even though, the occurrence of seizures has been observed in hemodialysis patients or patients with low eGFR [3,5–7,11,16,23]. It is important to mention that the EEGs done at our institution were all "routine EEG" with less than 30 min duration.

We excluded patients who were critical condition and who might require continuous EEG to detect subclinical seizures. Approximately 11.5% of our patients expired within six months of performing their EEG, this is probably due the fact that these patients had multiple underlying comorbidities including heart failure, cancer, and infectious diseases.

We found an association between having a low eGFR and the risk of having EEG abnormalities. This goes along with Gadewar et al observations of characteristic changes with increasing severity of CKD. They concluded that CKD patients without overt clinical signs of encephalopathy, can have subclinical or latent uremic encephalopathy, which can be detected with EEG [24].

In contrast to previous studies, we did not find a statistically significant relationship between sepsis and the risk of developing a seizure at 6 months (p = 0.245). This could be explained by our sample population, since our patients were all in non-critical condition at time of selection. Michael et al demonstrated that sepsis survivors faced a significant long-term risk of developing seizures, with a risk that was approximately 5 times higher than the general population. Even when compared to other hospitalized patients, those who had sepsis had a higher long-term risk of seizures [25]. Additional studies and longer follow up are needed to further study this association.

Looking at specific medication use in our population we highlighted a possible relationship between the use of carbapenems and the risk of death at 6 months (p = 0.059). The associated comorbidities can contribute to this higher risk but until this date no study has evaluated the long-term effects of carbapenems in the general population nor in CKD patients.

Finally, our study showed significant association between having an abnormal EEG and the risk of developing an epileptic seizure (p = 0.038) independently of the eGFR. If the EEG shows non-specific abnormalities the risk becomes 37%, whereas if epileptiform discharges are observed, this risk increases to 58%. According to the literature, EEG abnormalities following a new-onset seizure, particularly epileptiform abnormalities, are predictive of seizure recurrence [26]. It is believed that the brain is in a hyperexcitable condition at this time [27]. This raises many questions about the management of patients with an initial abnormal EEG and whether prophylactic antiseizure medications should be initiated.

Our study has few limitations that will be discussed. First, it included patients hospitalized at a major tertiary care center with a referral bias of having complicated medical issues so we cannot extrapolate our findings to other populations.

Even though we perform around 30 EEGs per month in hospitalized patients at our institution, most of them could not be included in the study, for social or logistic considerations or presence of exclusion criteria. Quantitative EEG analysis would have added a better understanding of the pathophysiology of the EEG changes in people with altered renal function but unfortunately it's not done routinely at our hospital.

In addition, although the questionnaire performed by phone

## Table 5

Effect of renal function on the occurrence of seizures at 6 months.

			EEG ABNORMALITY					ARCENIT								
			L UT	JEINI						AD3	LINI					
			n	NPV	95 %CI		SP	95 %CI		n	PPV	95 %CI		SE	95 %CI	
Total	Seizure at	А	23	100.0%	89.8%	100.0%	42.6%	30.1%	55.9%	31	81.6%	67.2%	91.4%	57.4%	44.1%	69.9%
	6 M	Р	0	0.0%			0.0%			7	18.4%	8.6%	32.8%	100.0%	70.8%	100.0%
eGFR CKD-EPI	Seizure at	Α	3	100.0%	46.4%	100.0%	33.3%	10.4%	65.2%	6	85.7%	49.9%	98.4%	66.7%	34.8%	89.6%
$\leq 30 \text{ ml/}$ min/m <sup>2</sup>	6 M	Р	0	0.0%			0.0%			1	14.3%	1.6%	50.1%	100.0%	14.7%	100.0%
$30 < eGFR \ CKD$ -	Seizure at	Α	2	100.0%	33.3%	100.0%	33.3%	7.7%	71.4%	4	80.0%	37.1%	97.7%	66.7%	28.6%	92.3%
EPI <= 60 ml/ min/m <sup>2</sup>	6 M	Р	0	0.0%			0.0%			1	20.0%	2.3%	62.9%	100.0%	14.7%	100.0%
eGFR CKD-EPI $>$	Seizure at	Α	18	100.0%	87.1%	100.0%	46.2%	31.3%	61.6%	21	80.8%	62.9%	92.3%	53.8%	38.4%	68.7%
60	6 M	Р	0	0.0%			0.0%			5	19.2%	7.7%	37.1%	100.0%	62.1%	100.0%
ml/min/m <sup>2</sup>																

A: absent, CI: confidence interval, NPV: negative predictive value, P: present, PPV: positive predictive value, SE: sensitivity, SP: specificity.

included specific and unique questions to all patients (or their family members), the incidence of seizures could have been falsely estimated given the limitations of the interviews and available objective information and at times the poor cooperation of family members to give further details. Reporting myoclonic jerks for example on follow up can be epileptic or metabolic in origin. A face-to-face structured evaluation, additional investigations, and longer follow up period are needed in subjects who developed seizures especially to distinguish development of acute symptomatic seizures from epilepsy.

## Conclusions

The routine EEG is a useful tool for predicting the risk of seizures at 6 months in hospitalized patients. In these subjects, we found that while eGFR and the incidence of seizures were not directly related, and independent of the eGFR, patients with abnormal EEG at baseline, were more likely to develop seizures in the future. On the other hand, even minor reduction in kidney function was associated with EEG changes.

Larger prospective studies with follow up EEG and structural clinical interview should be undertaken to further investigate the relationship between eGFR and the risk of having a seizure or developing epilepsy at long term.

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None.

#### **Declaration of interest**

None.

# Author contributions

Concept and design: Dr Abou Khaled.

Drafting of the manuscript and data analysis: Drs Abou Khaled and Matta.

Critical revision of the manuscript for important intellectual content: Dr Azar.

Data collection: Drs Hamza, Abi Nahed and Matta.

## **Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi. org/10.1016/j.ebr.2023.100615.

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