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Glomerular hyperfiltration in patients with severe trauma

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ABSTRACT

Background and objective: Augmented renal clearance or glomerular hyperfiltration (GHF) can significantly affect the clinical outcomes of renally eliminated drugs by promoting subtherapeutic drug exposure. The aggression suffered in patients who suffer severe trauma is a predisposition to manifest GHF and the identification of these patients remains a clinical challenge. The main objective of this study was to describe the prevalence of GHF in a cohort of critically ill trauma patients.

Materials and methods: Prospective observational study of a cohort of adult patients admitted after suffering severe trauma or polytrauma in the Anesthesiology ICU of the University Hospital of Albacete (Spain). Creatinine clearance (ClCr) was calculated in a 4-h urine collection sample at 24, 72 and 168 h after admission applying the formula; CrCl: [Diuresis in ml (urine/4 h) × Creatinine in urine (mg/dl)] ÷ [240 (minutes) × Creatinine in plasma (mg/dl)]. A CrCl above 130 mL/min was considered GHF. The analyses were performed with the statistical software R version 4.0.4.

Results: 85 patients were included. The median age of the patients was 51 years (IQR 26), 78.82% male. 68 patients were male (78.82%). 75.29% of the patients were polytraumatized. 61 patients (71.76%) presented GHF at some point in the CrCl determination. At 24 h of admission, 56.34% of the patients presented GHF with a mean CrCl of 195.8 ml/min, 61.11% of the patients presented it at 72 h with a mean CrCl of /min and 56.52% presented GHF at 168 h of admission with a mean CrCl of 207 ml/min. A significant positive relationship ($p = 0.07$) was found between GHF manifested at 72 h and at 168 h. We observed a statistically significant relationship between this phenomenon with younger ages, lower ISS scores and lower plasma creatinines.

Conclusions: GHF are a common condition in critically ill patients admitted for severe trauma. We recommend the use of CrCl to assess renal function and make dosage adjustments. Studies are required to understand the clinical impact of these phenomena on drug elimination and to be able to establish the ideal dosage in those cases.

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Hiperfiltración glomerular en el paciente traumático grave

Palabras clave:
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Hiperfiltración glomerular
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RESUMEN

Antecedentes y objetivo: El aclaramiento renal aumentado o hiperfiltración glomerular (HFG) puede afectar significativamente a los resultados clínicos de los fármacos eliminados por vía renal al promover la exposición subterapéutica al fármaco. La agresión sufrida en los pacientes que sufren trauma grave supone un predisponente a manifestar HFG y la identificación de estos pacientes sigue siendo un desafío clínico. El objetivo principal de este estudio fue describir la prevalencia de HFG en una cohorte de pacientes críticos traumatizados en la primera semana de ingreso.

Materiales y métodos: Estudio prospectivo observacional de una cohorte de pacientes adultos ingresados tras sufrir un trauma grave o politraumatismo en la UCI de Anestesiología del Complejo Hospitalario Universitario de Albacete (España). Se calculó el aclaramiento de creatinina (ClCr) en muestra de recolección de orina 4 horas a las 24, 72 y 168 horas de ingreso aplicando la fórmula ; ClCr: [Diuresis en ml (orina/4 h) × Creatinina en orina (mg/dl)] ÷ [240 (minutos) × Creatinina en plasma (mg/dl)]. Un CrCl por encima de 130 ml/min fue considerado HFG. Los análisis se realizaron con el software estadístico R versión 4.0.4.

Resultados: Se incluyeron 85 pacientes. La edad mediana de los pacientes fue de 51 años (RIQ 26), 78,82% varones. 68 pacientes fueron varones (78,82%). El 75,29% de los pacientes fueron politraumatizados. 61 pacientes (71,76%) presentaron HFG en algún momento de la determinación del ClCr. A las 24 horas de ingreso el 56,34% de los pacientes presentaron HFG con ClCr medio de 195,8 ml/min, el 61,11% de los pacientes lo presentaba a las 72 horas con ClCr medio de 186 ml/min y el 56,52% presentaban HFG a las 168 horas de ingreso con ClCr medio de 207 ml/min. Se encontró una relación positiva importante (p = 0,07) entre la HFG manifestada a las 72 horas y a las 168 horas. S observó relación estadísticamente significativa entre este fenómeno con edades mas jóvenes, puntuaciones ISS mas bajas y creatininas plasmáticas mas bajas.

Conclusiones: La HFG es una condición frecuente en los pacientes críticos ingresados por trauma grave. Recomendamos el uso del ClCr para evaluar la función renal y realizar ajustes posológicos. Se requieren estudios para comprender el impacto clínico de estos fenómenos sobre la eliminación de fármacos y poder establecer la dosificación ideal en tales casos.

Introduction

Optimizing drug dosing in critically ill patients continues to be a challenge in clinical practice within Intensive Care Units (ICU).

Standard treatment guidelines includes the identification of patient-dependent factors that require dose reduction, such as renal insufficiency. Many dosing schedules have been extrapolated from healthy volunteers or outpatients, without considering the pathophysiology[1] or clinical heterogeneity.

A key pharmacokinetic (PK) variable of interest is drug clearance. Previous data have shown markedly elevated dug clearance in subsets of critically ill patients.[2] This phenomenon has been termed enhanced renal clearance[3,4] and can significantly affect the clinical outcomes of many renal eliminated agents by promoting subtherapeutic drug exposure.[5]

The identificatio of patients with increased renal clearance or glomerular hyperfiltration (GHF) remains a clinical challenge. We currently have formulas based on mathematical estimates of glomerular filtration that were designed primarily for use outside the ICU and are focused on the detection of decreased glomerular filtration. Their application in this clinical setting has many limitations.[6]

The main objective of this study was to describe the prevalence of GHF in a cohort of critically ill trauma patients during the first week of admission. The secondary objectives were to observe its evolution over time and to associate physiological characteristics and disease severity with GHF in this cohort of patients.

Study design

This is a prospective observational study of a cohort of adult patients admitted after suffering severe trauma or polytrauma in the area of Anesthesiology in the ICU of the Complejo Hospitalario Universitario de Albacete (Spain). The inclusion criteria were to be 18 years of age or older, with bladder catheter in place, without documented history of renal failure, not to have received renal replacement therapy during the study period, and not to have died within the 24 h after admission. The study was approved by the Research Ethics Committee of the center

Table 1 – Baseline characteristics of patients and their association with glomerular hyperfiltration.

	Study group $n=85$	GHF $n=61$ (71.76%)
Age, years, median (IQR)	51 (26)	46 (42) $p=0.015$
Male sex, n (%)	67 (78.82%)	74.6% $p=0.4$
Female sex, n (%)	18 (21.18%)	61.1% $p=0.4$
BSA in m^2, mean (SD)	1.87 (0.19)	
MBP, mean (SD) mmHg	85 (9.11)	
HR, mean (SD) bpm	86.8 (17.9)	
SOFA, median (IQR)	4 (5)	5 (4) $p=0{,}57$
Noradrenaline, *n* (%)	24 (33.8%)	10 (27.03%) $p=0.19$
Furosemide, *n* (%)	19 (25.68%)	7 (17.5%) $p=0.15$
Admission plasma Cr, mg/dl, median (IQR)	0.87 (0.36)	
Mean Cr, mg/dl (IC 95 low-IC95 high)		
24 h	0.75 (0.69–0.8)	0.75 (0.69–0.8) $p<0.05$
72 h	0.78 (0.72–0.85)	0.78 (0.72–0.85) $p=0$
168 h	0.64 (0.55–0.74)	0.64 (0.55–0.74) $p<0.05$
Polytraumatized, *n* (%)	64 (75.29%)	68.75% $p=0.42$
Number of traumas, median (RIQ)	2 (1)	
Days of admission, median (RIQ)	5 (8)	

ClCr, creatinine clearance; Cr, creatinine; HR, heart rate; GHF, glomerular hyperfiltration; bpm, beats per minute; mmHg, millimeters of mercury; BPM, beats per minute; BHR, beats per minute; IQR, interquartile range; BSA, body surface area; MBP, mean arterial blood pressure; HR, heart rate; SD, standard deviation.

Table 2 – Association of glomerular hyperfiltration at each time point with the patientsĺesion balance.

	n (%)	GHF 24 h	GHF 72 h	GHF 168 h	GHF at some point
Polytraumatized					
Yes.	64 (75.29%)	72.5% $p=0.8$	78.79% $p=0.5$	76.92% $p=0.65$	68.75% $p=0.42$
No	21 (24.71%)	27.5% $p=0.8$	21.21% $p=0.5$	23.08% $p=0.65$	80.95% $p=0.42$
Type of trauma					
TCE	42 (49.41%)	19 (47.5%) $p=0.8$	20 (60.61%) $p=0.5$	11 (84.62%) $p=1$	71.42% $p=1$
Abdominal	19 (22.35%)	6 (15%) $p=0.08$	7 (21.21%) $p=1$	3 (23.08%) $p=0.23$	68.42% $p=0.93$
Toracic	54 (63.53%)	22 (55%) $p=0.16$	20 (60.61%) $p=0.87$	7 (53.85%) $p=0.68$	66.66% $p=0.25$
Raquimedular	38 (44.71%)	21 (52.5%) $p=0.23$	13 (39.39%) $p=8.87$	5 (38.46%) $p=1$	73.68% $p=0.91$
Musculoskeletal.	48 (56.47%)	5 (38.46%) $p=1$	21 (63.64%) $p=0.38$	8 (61.54%) $p=1$	75% $p=0.6$

GHF, glomerular hyperfiltration; TBI, traumatic brain injury.

where the study was performed (project n.º 2018/10/107) and clinical data and biological samples were collected with the informed consent of each patient or their representative.

The sample size of 85 patients, was calculated based on the main objective and having as reference previous work on glomerular hyperfiltration (GHF) performed in patients in the ICU setting with various reasons for admission.[3,4,7,8]

The collection period began in January 2019 and patients were included sequentially except between March and June 2020 due to the unit's care overload in the first wave of covid-19. Three patients who met inclusion criteria were not included in this interval.

Variables, material and method

On admission, the following variables were collected in each patient: demographic data (age, gender, weight, height), type of trauma or polytrauma, *Sequential Organ Failure Assessment Score* (SOFA) score,[9] ARCTIC scale score,[7] *Injury Severity Score* (ISS) score,[10] vital signs and first determination of plasma creatinine on arrival at the hospital.

As an indicator of glomerular filtration rate (GFR), creatinine clearance (ClCr) was calculated at 24, 72 and 168 h of admission. The urine sample was collected during a period

Table 3 – Relationship of the positive ARCTIC *score* with the detection of glomerular hyperfiltration.

	GHF	No GHF	*p*
ARCTIC ≥ 6			
At any point in time	75.5%	50%	0.002
24 h	80%	58%	0.08
72 h	72.7%	38.1%	0.03
168 h	69.2%	50%	0.42

GHF: glomerular hyperfiltration.

of 4 h, plasma creatinine values were collected as part the analytical tests performed as standard clinical practice in the ICU and the usual formula was applied[11]; ClCr: [Diuresis in ml (urine/4 h) × Creatinine in urine (mg/dl)] ÷ [240 (minutes) × Creatinine in plasma (mg/dl)].

On days of determinations required for ClCr, data were collected for the last 24 h that included administration of furosemide or need for noradrenaline drugs as a vasopressor drug.

Plasma and urine creatinine determinations were performed in the c 702 module of a Roche/Hitachi Cobas 8000. Creatinine was determined by a kinetic colorimetric method based on the Jaffé method.

A CrCl above 130 ml/min was considered GHF.[3,4,6,12]

Statistical analysis

Descriptive analysis was performed using the usual measures of central tendency and dispersion (mean and standard deviation, or median and interquartile range). For bivariate analysis, the Student *t*-test was used for parametric variables and the Mann-Whitney *U* test for nonparametric variables. Fisher's exact test and the chi-square test were used to compare proportions. A p value ≤0.05 was chosen statistical significance level.

All analyses were performed with R statistical software version 4.0.4.

Results

General characteristics

The characteristics of the 85 patients included in this study are shown in Table 1. Tables 2 and 3 show the types of trauma motivating admission to the ICU and their relationship with GHF at each time point.

The median age of the patients was 51 years (IQR 26), 68 patients were male (78.82%). A 75.29% of patients were polytraumatized, defined as having two or more severe (life-threatening) traumatic injuries, with a median number of traumas of 2, median ISS of 25 and SOFA on admission of 4. A 33.8% of patients required noradrenaline to achieve the blood pressure target and the median ICU stay was 5 days.

A total of 61 patients (71.76%) had GHF at some point during the determination of ClCr.

During the first 24 h of admission, 56.34% of patients had a mean ClCr of 195.8 ml/min. At 72 h, 61.11% of patients had a mean ClCr of 186 ml/min, and at 168 h a 56.52% had mean ClCr of 207 ml/min, all values of GHF (Fig. 1).

We studied whether there were differences in the distribution of GHF according to its previous presence and it was observed a mild positive relationship ($p = 0.38$) of GHFal between determinations at 24 and 168 h and a close to significant positive relationship ($p = 0.07$) between GHF manifested at 72 h and at 168 h, suggesting a dependence of positive GHF at 168 h on its presence at 72 h.

Grades of GHF were established according to the values of ClCr to categorize patients and bear a resemblance to the classification with the classic categories of renal failure.[12] Grade I GHF included ClCr from 131 to 164 ml/min; grade II GHF included ClCr from 165 to 200 ml/min, and grade III GHF included ClCr greater than 200 ml/min. In the determinations at 168 h, patients had a higher percentage of grade III GHF (61.54%) than in the rest of the admission days analyzed (Fig. 2 f).

It was also analyzed the clinical-biological factors associated with a higher prevalence of GHF and found a statistically significant relationship between this phenomenon and younger age, lower ISS scores and lower plasma creatinine (Table 1). No statistically significant relationship was found between GHF and the patient's different injuries or with the administration of noradrenaline or furosemide (Tables 1 and 2).

In this cohort of patients the ARTIC *score* presented a sensitivity of 75.5% and a specificity of 50% for the detection of GHF (in the original study: S 84%, E 68%). It was found to be less sensitive for detecting GHF at the 72 h time point, this observation being statistically significant (Table 3).

Discussion

In this exploratory study we found that GHF is a relatively frequent condition in critically ill patients who suffer severe trauma. It is manifested mainly on the third day of admission, and in cases in which it develops there is a high possibility that this condition will be maintained for one week.

The pathophysiology of GHF in the critically ill patient is currently unclear. It has been observed that critically ill patients may develop a hyperdynamic/hyperkinetic state, leading to increased ClCr and renal elimination of certain drugs.[1] This is consistent with studies in large animal models of gram-negative sepsis, where an elevated cardiac index, low systemic vascular resistance and increased major organ blood flow have been demonstrated.[13] As we did not measure cardiac output in this study, we cannot state that an increase in this parameter causes GHF due to its physiological effects on renal perfusion.

The application of intensive fluid resuscitation and vasopressor support are additional factors leading to this hyperdynamic state,[14,15] and many equivalences can be drawn with pregnancy, where similar cardiovascular changes are associated with increased renal blood flow and glomerular filtration.[16]

Based on the few published studies we can observe that, in the absence of established acute kidney injury, the innate hemodynamic response to severe traumatic insult, along with

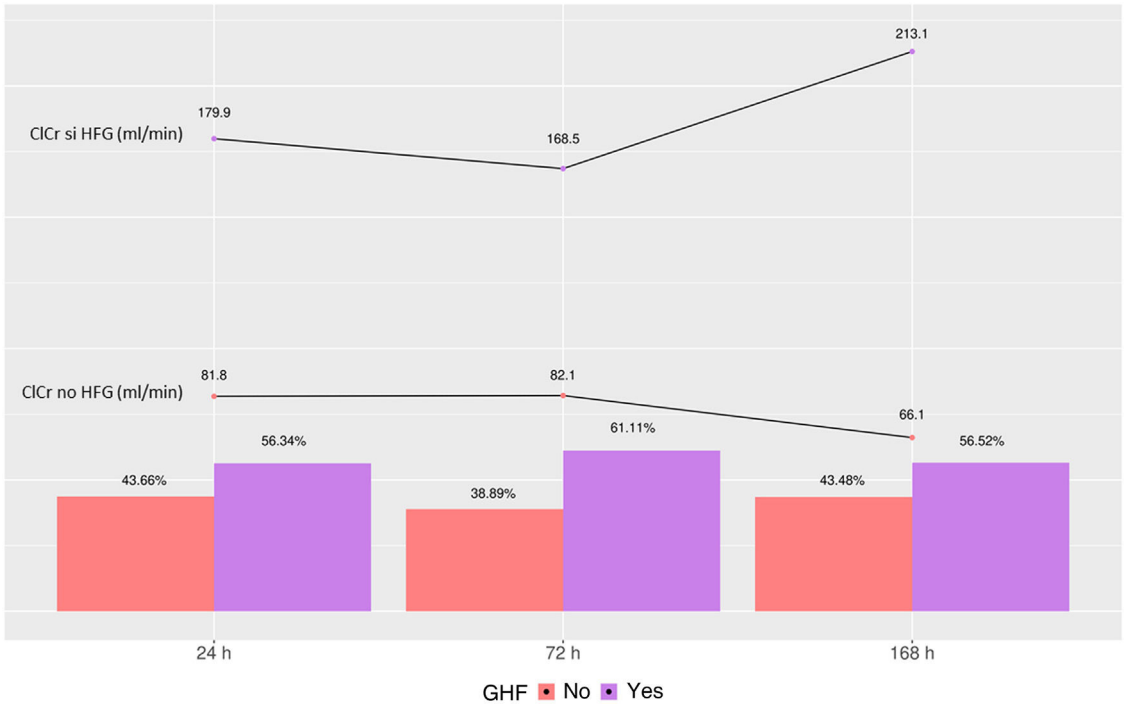

Figure 1 – Prevalence of glomerular hyperfiltration at each time point and creatinine clearance in ml/min in both groups. ClCr: creatinine clearance; GHF: glomerular hyperfiltration; h: hours.

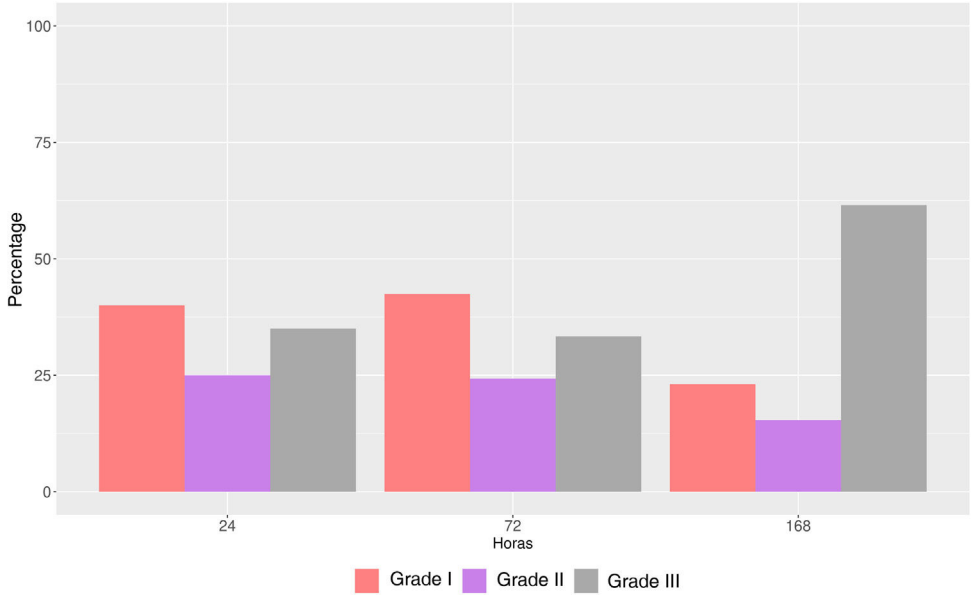

Figure 2 – Percentage of patients classified according to the degrees of glomerular hyperfiltration proposed by the authors.

common clinical interventions involving resuscitation and stabilization, may promote increased solute delivery to the kidneys and with a subsequent increased renal elimination.

Until now, GHF in ICU has not been considered as something of relevant clinical importance, possibly due to the fact that this physiological manifestation is part of a concept normally used in the study of chronic pathologies.[15]

Recently, the use of predictive GHF *scores* applied to the critically ill patient has been proposed, such as the ARC *score* or ARCTIC *score*,[7] which allow the identification of patients at risk of GHF and can help us to make appropriate interventions (e.g., calculate a ClCr, or use more aggressive antibiotic dosing regimen, etc.). In this study we used the ARCTIC and it was found that the sensitivity and specificity of this *score did* not match in our cohort to that published in the original validation study (the original showed sensitivity of 84% and specificity of 68%).

In routine clinical practice, renal function assessment is based on the determination of plasma creatinine, using formulas based on indirect estimation. The most commonly used

are those of Cockcroft and Gault[17] and the MDRD[18] and have been validated in several studies outside the ICU setting.[19] Serum creatinine does not reflect the same degree of renal function in all patients as it is influenced by a series of factors such as age, sex, race, body surface area, type of diet, use of certain drugs.[20,21] To avoid these limitations, in the present study we have chosen to use the measurement of creatinine clearance from urine collection, which reflects more accurately the glomerular filtration rate.[11,21] The importance of measuring clearance is not only for better assessment of renal function, but also for early detection of patients who are classified as normal by isolated determination of plasma creatinine.[3,20,21]

A limitation of our procedure of measurement may derive from the fact that it is based on morning urine samples collected during periods of 4 h instead of 24 h. This may raise objections, since the results may be influenced by chronobiological factors pertaining to diurnal life, variations in ClCr. However, samples collected over short periods of time have been validated in terms of their results,[22,23] bring the advantage of minimizing errors related to sample collection, and allow early reassessment of glomerular filtration without entailing delay in drug titration.

Another limitation of the study may be to have considered the cutoff of 130 ml/min to categorize patients with GHF. We found that the reference interval for determining an abnormal increase in ClCr is broad[3,24] and therefore defining a value for GHF is not firmly established. We decided to establish this cutoff point as it is the most consistent in the literature.

In the present this study, it was decided to categorize the values of ClCr by intervals as a scheme similar to that established for the diagnosis of the degree of renal failure. We are aware of the fact that this categorization is not supported by the literature, but it can serve as a starting point for new studies.

Even taking into account the aforementioned limitations, and leaving aside the definition of GHF, we consider it useful to study the repercussions that an increase in renal clearance can have on drug dosing in critically ill patients, specifically the risk of under-dosing due to improved drug elimination. In this regard, the monitoring of therapeutic drug concentrations is of special interest in those cases where it is available and we found an important limitation derived from the type of critical patient population studied; on admission, their usual medication of these patients is suspended and they receive limited treatment that focuses on beta-lactam antibiotics for their lesions, analgesics, sedatives on occasions and anticomantibiotics (usually levetiracetam) in the cases of neurocritical patients in which they are indicated. Monitoring of these drugs with a high safety profile is usually not available in daily clinical practice.

We do not currently have recommendations for dose adjustment in the critically ill patient with GHF and must take into consideration that not only will this phenomenon be a cause of potential therapeutic failure due to failure to achieve adequate plasma concentrations; increased capillary permeability, water overload, rapid variations in volume of distribution, the use of vasoactive drugs and altered excretory organ function will significantly affect the normal pharmacokinetic (PK) profile of many agents.[5,25,26]

Recently, strategies have been proposed to optimize drug exposure through more frequent dosing, higher doses or the use of continuous or extended infusions.[2,27]

Conclusions

We found that GHF phenomenon is a frequent condition in critically ill patients admitted for severe trauma.

The formulas for estimating glomerular filtration rate have not been rigorously validated in the critically ill patient; we recommend the use of ClCr to assess renal function and make dosing adjustments.

Studies are required to understand the clinical impact of these phenomena on drug elimination and to be able to establish the ideal dosage in such cases.

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Conflict of interest

None.

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