TITLE

Prevalence of acute kidney injury in intensive care units: the COFRADE point-prevalence multicentre study

AUTHORS

Manuel E. Herrera-Gutiérrez, PhD. Associate professor, University of Malaga Medical School. Intensivist. ICU, University Hospital Carlos Haya, Málaga, Spain.

Gemma Seller-Pérez, PhD. Intensivist. ICU, University Hospital Carlos Haya, Málaga, Spain.

José A. Sánchez-Izquierdo-Riera, PhD. Intensivist. Head of Clinic. Hospital 12 de Octubre, Madrid, Spain.

Javier Maynar-Moliner, MD. Intensivist. Head of Clinic. Hospital Santiago, Vitoria, Spain.

On behalf of the COFRADE investigators group.

ACKNOWLEDGEMENT

The COFRADE study was endorsed by the Spanish Society of Intensive Care Medicine (SEMICYUC).

NUMBER OF WORDS IN ABSTRACT

250

NUMBER OF WORDS AND ABSTRACT IN MANUSCRIPT

3473

Corresponding author

Manuel E. Herrera-Gutiérrez, PhD. Associate professor.

ICU, University Hospital Carlos Haya, Málaga, Spain.

29010, Malaga, Spain

mehguci@gmail.com

Con formato: Izquierda: 3 cm, Derecha: 3 cm, Arriba: 2,5 cm, Abajo: 2,5 cm, Ancho: 20,99 cm, Alto: 29,7 cm, Distancia del encabezado desde el borde: 1,25 cm, Distancia del pie de página desde el borde: 1,25 cm

INVESTIGATORS OF THE COFRADE STUDY GROUP:

Hospital Clínic. Barcelona:

Servicio de Nefrología: NS Pérez.

ICU hepatology: J Acevedo, A Más, M Castro.

ICU general: JM Nicolás.

ICU surgery: E Zavala (IDIBAPS), R Adalia, FJ Tercero.

ICU nephrology: E Poch, N Serra.

ICU cardiology: X Bosch-Genover.

ICU respiratory: JR Badia.

ICU heart surgery: R Cartana.

ICU anesthesiology: J Fontanals.

Hospital Clínico San Carlos. Madrid.

ICU: F Ortuño-Andériz.

Hospital Costa del Sol. Málaga.

ICU: MI Fernández-García.

Hospital de Alcorcón. Madrid.

ICU: A Núñez-Reiz.

Hospital de Cruces. Bilbao. Osakidetza.

ICU anesthesiology: N Lekerika.

ICU medical: A Sánchez.

Hospital de Guadalajara. Guadalajara.

ICU: C Benito Puncel, JM Borrallo.

Hospital de la Santa Creu i San Pau. Barcelona.

ICU: A Roglán Piqueras, M Rodríguez-López.

Hospital del Norte. Madríd.

ICU: M González-Arenas, M Paloma.

Hospital del Sureste. Madríd.

ICU: M Ochoa-Calero, P Albert-de-la-Cruz, M Cruz-Tejedor.

Hospital del Tajo. Madríd.

ICU: F Ballesteros-Ortega.

Hospital Fundación Jiménez Díaz. Madrid.

ICU: MA Alcalá-Llorente, C Pérez-Calvo, G Oeding-Angulo.

Hospital General Universitario Asociado. Castellón.

ICU: S Mas-Font, R González-Luis, A Ferrándiz-Sellés.

Hospital General Yague. Burgos.

ICU: MJ López-Pueyo, L LLata-Rodríguez, ME Perea Rodríguez.

Hospital Germans Trias i Pujol. Badalona

ICU: TM Tomasa-Irriguible.

Hospital Ramón y Cajal. Madrid.

ICU anesthesiology: A Candela-Toharia.

ICU medical: JA Liétor-Villajos.

Hospital Severo Ochoa. Madríd.

ICU: J López-Martínez, N Chamorro-Borraz, J Suárez-Saiz.

Hospital Torrecárdenas. Almería.

ICU: JA Ramos-Cuadra, A Calderón-Rodríguez, R Rodríguez-Castaño.

Hospital Universitario 12 de Octubre. Madrid.

ICU: JL Flordelis-Lasierra, A Mohedano-Gómez, L Terceros.

ICU (UCP): JL Pérez-Vela.

Hospital Universitario Carlos Haya. Málaga.

ICU: R Lozano-Saez, R Olalla-García, R Aguiar.

Hospital Universitario de Canarias. Tenerife.

ICU: L Lorenzo-de-la-Peña, N Pérez-Martínez.

Hospital Universitario Dr. Peset. Valencia.

ICU: R Zaragoza, E Casanoves-Laparra, Y Montoro-Lozano.

Hospital Universitario Infanta Cristina. Badajoz.

ICU: M Robles-Marcos, R Almaraz-Velarde, MV Trasmonte-Martínez.

Hospital Universitario La Paz. Madrid.

ICU: A Garcia-de-Lorenzo, M Sánchez, E Perales.

Hospital Universitario Puerta del Mar. Cádiz.

ICU: R Sierra-Camerino, AC Sánchez-Rodríguez.

Hospital Vega Baja. Orihuela.

ICU: C Giménez-Esparza-Vich, D Pérez-Martínez, C Portillo-Requena.

Hospital Universitario Virgen de la Arrixaca. Murcia.

ICU: J Ros-Martínez, C Llamas-Lázaro.

Hospital Virgen de la Victoria. Málaga.

ICU: D Daga-Ruiz, J Vidal-Hernández-Rodríguez.

Hospital Virgen de las Nieves. Granada.

ICU traumatology: F Guerrero-López.

Hospital Universitario Virgen de Valme. Sevilla.

ICU: D Herrera-Rojas, A Úbeda-Iglesias, T Contreras-del-Pino.

Hospital Virgen del Rocío. Sevilla.

ICU: R Hinojosa-Pérez.

Hospital Universitario Virgen Macarena, Sevilla

ICU: S Ibáñez-Cuadros, A Arenzana-Seisdedos.

Hospital Xeral. Lugo.

ICU: L Álvarez-Montero, V Nespereira-Jato, O Saornil-Agote.

FINANCIAL DISCLOSURE AND CONFLICTS OF INTEREST

All the authors state that they have no relevant conflicts of interest. This study was not funded and the expenses were covered by departmental funds at the first author institution.

ABSTRACT

Purpose. To measure point-prevalence of kidney dysfunction (KD) in the intensive care setting.

Materials and Methods. Point-prevalence, single-day, prospective study. Out of 919 patients present in 42 ICUs two specific days (September 2009 and March 2010), 832 cases were included. Mild-KD was defined as a measured creatinine clearance (CrCl) 90–60 mL·min^{-1}*1.73 m^{-2} and severe-KD as a CrCl below 60.

Results. Prevalence of mild-KD was 15.9/100patient/day (13.5–18.5) and severe-KD was 42.4/100/day (39.1–45.8). We considered as having a low probability of suffering kidney dysfunction those patients without chronic kidney disease (CKD), AKIN stage 0, and a Crs<1.2 mg/dL but among them (557 patients) 18.1% (15.2–21.6) had mild-KD, and 24.2% (20.9–28) severe-KD.

ICU mortality was 10.6% (7.81–14.4) for patients without dysfunction, 16.6% (11.2–24) with mild-KD, and 29.7% (25.2–34.7) (p<0.001) with severe-KD, with a relative risk for severe-KD against no KD of 2.54 (1.90–3.40).

In 54.3% patients at least 1 renal insult was reported. One nephrotoxic drug was administered to 34.4%, and 2 or more to 14.9% patients, with a lower frequency among those with CKD (30.6% vs 50.8%, p<0.05).

Conclusions. Each day of study, more that half of the patients admitted to the ICU showed some derangement in kidney function. Over 25% of patients not fulfilling KD criteria by serum creatinine or AKIN showed in fact a severe KD and this finding was associated to higher mortality. More than 50% of the patients admitted to the ICU were subjected to at least 1 renal insult.

KEYWORDS

Kidney dysfunction. Kidney injury, acute. Prevalence studies. Outcome Measures. Nephrotoxics. Creatinine clearance.

Eliminado: /(

Con formato: Superíndice , Resaltar

Eliminado: ·

Eliminado:)

Eliminado: 6.7

INTRODUCTION

Incidence studies are a useful tool for the characterization of risk factors and outcomes because they are supposed to include all the cases appearing during the period under study, being these cases then followed until the required outcome is met. But when the problem under investigation presents with a high incidence or a prolonged course these studies are costly and difficult to perform. Prevalence studies do not let us measure those end-points but, by enrolling all the patients detected in a specific period of time (new or already present cases) and considering only a limited follow-up period, are easier to perform and can be useful for the evaluation of the impact of these clinical problems on health systems and for developing preventive strategies.

Since acute kidney injury (AKI) presents with a low incidence and a rapid time course in the general population, prevalence studies have not been considered necessary for this condition. However, a high incidence (1) and a relatively prolonged course (compared to the length of stay) are observed among intensive care unit (ICU) patients and prevalence studies could provide useful information for the implementation of preventive measures and resource allocation planning in this setting.

Critically ill patients develop kidney dysfunction (KD) under different circumstances and special conditions present in the ICU (e.g., hemodynamic alterations or use of nephrotoxic drugs) and secondary prevention measures are especially relevant in these particular scenarios. Published studies on KD incidence in the ICU thus far are not considered definitive for several reasons. First, these studies did not consider that some patients might experience multiple events. Second, it has been demonstrated that the use of creatinine clearance (CrCl) to estimate glomerular filtration rate (GFR), instead of serum creatinine (Crs) or RIFLE/AKIN systems (2, 3), could result in significantly higher incidence rates than those previously reported (4, 5).

We hypothesize that the presence of KD in the ICU (with its potential impact in workload and cost of care) is significantly greater than considered so far, and that a prevalence study would provide an accurate measure of its effect in the ICU. However, to the best of our knowledge, and with only one study suggesting that one-year prevalence may reach 70% (6), no studies on point-day prevalence have been published thus far. Our aim was in the first place to define the

percentage of patients admitted in our units that presented KD the days under study and then how many of them would have gone undetected by the usual methods of diagnosis (i.e. serum creatinine and AKIN classification). To minimize the risk of underestimating the incidence of AKI, in this study we opted for a direct CrCl measurement as diagnosis of KD.

SUBJECTS AND METHODS

COFRADE study refers to "COrte de prevalencia de disFunción RenAl y DEpuración en críticos" [point-prevalence of kidney dysfunction and renal replacement in critically ill patients]. It is a single-day, observational, prospective, and multicentre study aimed at measuring point-prevalence of KD in ICU. The study was conducted in 2009, when selected ICUs in Spain were invited to participate. During initial contact with the investigators following their ICUs enrolment, and before revealing the full study protocol, investigators were asked to complete a survey on hospital and ICU characteristics, KD detection and renal protection methods used and renal replacement therapies (RRT) implemented (7). The unit was then enrolled in the study following approval from its corresponding local ethics committee. Two distinct days, 6 months apart (September 2009 and March 2010), were previously assigned for all participating units. All patients already present in the participating units the day of study were enrolled in the study and the only defined exclusion criteria were: age below 14 years; end-stage kidney disease under RRT; and refusal of the patient, or their next of kin, to sign the informed consent form.

Eliminado: The data for all patients already present or admitted to those units on these specific days were included in the study.

The following data were reported: demographic data (age, gender, height, weight), past medical history, cause of ICU admission (medical, surgical, cardiac surgery, trauma, solid organ transplant, coronary), hospital stay prior to admission, illness severity level at ICU admission (APACHE II and SOFA at admission) and previous kidney function (baseline Crs levels, Crs at ICU admission). For the analysis, the SOFA score at admission and the day of study were calculated excluding renal failure criteria.

The day of study we registered physiological and analytical data, diuresis, Crs, RRT, vasopressor drugs usage, nephrotoxic drugs administered (aminoglycosides, glycopeptides, colistin, amphotericin, cotrimoxazole, non steroidal anti-inflammatory drugs [NSAID], or angiotensin-converting-enzyme inhibitors) and those variables known to affect kidney function (hypotension defined as mean blood pressure below 60 mmHg sustained for more than 1 h, rhabdomyolysis and use of diuretics). The use of radiography-contrast was considered for the

previous 72 hours. Urine samples were collected for 2 hours and used to measure creatinine levels. Investigators were not encouraged to calculate CrCl, nor did the study guidelines specifically request this data. Similarly, assessment of AKIN criteria was not requested, but was evaluated during statistical analysis. Patients were followed-up until hospital discharge. After follow-up completion, all reports were scanned, and participating centres were asked to rescue missing data if possible.

The main variable in this study was kidney function, evaluated through measurement of CrCl in urine samples collected within 2 hours, and adjusted to the body surface area. This method has been previously validated for the ICU setting (8). Two different levels of KD were defined for data analysis: mild KD (mild-KD) for CrCl of 90–60 $mL*min^{-1}*1.73\ m^{-2}$, and severe (severe-KD) for CrCl below 60 $mL*min^{-1}*1.73\ m^{-2}$, in accordance with previously defined criteria for chronic kidney dysfunction (9).

Being a point-prevalence study, AKIN stage the day of study was computed taking under consideration the baseline Crs instead the Crs of the previous 48 hours in order to avoid missing those patients that had developed AKI earlier and should then go undetected. For baseline creatinine the lowest measure present in the medical records during the previous six months was considered; when unknown and in the absence of CKD history, MDRD-derived creatinine was used. Those patients under RRT the day of study were included in the AKIN-3 stage and the severe-KD group. Chronic kidney disease (CKD) was considered when specifically stated in the medical records of the patient. Additionally, patients without antecedents of CKD, AKIN stage 0 classification, and Crs <1.2 mg/dL were considered as having a low probability of KD (lowpr-KD).

Statistical analysis

The SPSS version 18.0 package was used for data analysis. Data are presented as (mean, 95% confidence interval [CI] of mean), (median, interquartile range [IQR]), or number (%, 95% CI of proportion). Confidence interval for a proportion was calculated using the calculator at http://www.graphpad.com/quickcalcs/.

A Kolmogorov-Smirnov test was performed and showed that variables were not normally distributed; therefore, nonparametric tests were used. For univariate analysis, the Mann-Whitney test, Kruskal-Wallis test, or Fisher's exact test were used as appropriate. All tests were

Eliminado: /(
Con formato: Superíndice , Resaltar
Eliminado: -
Con formato: Superíndice , Resaltar
Eliminado:)
Eliminado: /(
Eliminado: -
Con formato: Superíndice , Resaltar
Eliminado:)
Con formato: Superíndice , Resaltar

Eliminado: The only defined exclusion criteria were: age below 14 years; end-stage kidney disease under RRT; and refusal of the patient, or their next of kin, to sign the informed consent form. ¶

two-tailed, using $p < 0.05$ as the level of significance.

Risk factors for KD and ICU mortality were evaluated through relative risk (RR) and through multivariate analysis computing independent odds ratios by backward stepwise logistic mode. All variables in the univariate analysis with a significance level below 0.15 were included. Being this is a prevalence study, not suited for outcome analysis, we did not intend to define the best predictive model and all the variables were maintained in the final model if the odds ratio was statistically significant ($p < 0.05$). Results are only presented for significant variables, as odds ratio (OR, 95% CI of OR) and p.

Ethical issues

This was an observational study. No directions were given for any changes in the management of patients. Investigators were not in any way encouraged to specifically evaluate kidney function but to generally report on how their patients were managed. The only interference inflicted by this study was the collection of urine samples for 2 h and the measurement of creatinine levels in serum and urine. Enrolment in the study was never considered an indication for the insertion of a urinary catheter.

The approval of each centre's Ethics Committee was required. The obligation of obtaining the patient's signed informed consent was based on each local committee's decision.

RESULTS

A total of 42 ICUs in Spain (32 hospitals) were included, comprising 826 ICU beds. The profiles and results of the preliminary survey have been previously published (7).

We included 919 patients, 536 (58.3%) as part of the first day study and 383 (41.7%) the second day study, 6 months later. None of the patients abstracted data for both time-points. All variables studied were similar in both populations (separated time-points) except for the use of cotrimoxazole (6 patients [1.1%] from the first day study vs 12 patients [3.1%] from the second day study, $p = 0.05$) and norepinephrine (132 patients [24.6%] from the first day study vs 68 patients [17.8%] from the second day, $p < 0.05$).

We collected enough data to calculate CrCl and detect KD in 832 patients. The remaining 87 patients (9.5%), excluded from the analysis, had a significantly different profile than those ultimately included (Table E1). Among the 832 patients analysed, 62 (7.5%, 5.9–9.5) reported

the antecedent of CKD, comprising a group with a significantly different profile from patients who did not present this antecedent (Table E2). The study flow chart is presented in the Figure E1.

The prevalence of mild-KD (CrCl: 90–60) was 15.9 cases out of 100 patients/day (95% CI 13.5–18.5; n = 132) and that of severe-KD (CrCl < 60) was 42.4 cases out of 100 patients/day (95% CI 39.1–45.8; n = 353). Only 347 patients (41.7%) had a normal CrCl, and 68 patients (8.2%) were under RRT on the day of the study (Figure 1). Differences between patients according to kidney function are presented in Table 1.

According to the AKIN criteria, 607 (73%) patients were classified as AKIN-0, 42 (5%) as AKIN-1, 103 (12.4%) as AKIN-2, and 80 (9.6%) as AKIN-3. Among the 607 AKIN-0 patients, 110 (18.1%) in fact presented a mild-KD, and 169 (27.8%) a severe-KD dysfunction. Three AKIN-1 patients (7.1%) presented mild-KD, and 38 (90.5%) presented severe-KD; fifteen AKIN-2 patients (14.6%) presented mild-KD, and 74 (71.8%) presented severe-KD and finally, 4 AKIN-3 patients (5%) had mild-KD, and 72 (90%) had severe-KD (Figure 2).

We then analysed the lowpr-KD group that included 557 (66.9%) patients, 236 (42.3%, 38.3–46.5) of whom already presented KD: 101 (18.1%, 15.2–21.6) mild-KD, and 135 (24.2%, 20.9–28) severe-KD.

In 452 (54.3%) patients, at least 1 renal insult (nephrotoxic drugs, hypotension, rhabdomyolysis, or contrast radiography) was reported on the day of the study, which was significantly lower in patients with CKD (40.3% vs 55.5%, p < 0.05). Nephrotoxic drug analysis showed that a single drug was administered to 286 (34.4%) patients, and 2 or more drugs were administered to 124 (14.9%) patients, with a lower frequency observed among patients with CKD (30.6% vs 50.8%, p < 0.05). NSAIDs were administered to 155 (18.6%) patients for the whole population but only to 5 (8.1%) with CKD (p < 0.05). Then we focused on the lowpr-KD group that already had severe-KD and detected that 47 out of 135 (34.8%) had received at least 1 nephrotoxic drug, and 25 (19.2%) had received at least a dose of NSAIDs.

Overall ICU mortality was 19.7% (17.2–22.6, n=164). Higher mortality was observed among patients with CKD (38.7%, 27.6–51.2), compared to patients without this antecedent (18.2%, 15.6–21.1; p = 0.001), with a RR estimated at 2.23 (1.59–3.14). Mortality rates in patients according to level of KD were 10.6% (7.81–14.4) without dysfunction (reference group for

Eliminado: 6.7

Eliminado: ,

comparisons), 16.6% (11.2–24, p = 0.087) with mild-KD, and 29.7% (25.2–34.7, p < 0.001) with severe-KD, with a RR for severe KD estimated at 2.54 (1.90–3.40) (Figure 3). Mortality was 14.8% (CI 12.2–17.9) among AKIN-0 patients (reference group for comparisons), 21.4% (CI 11.5–36.2, p = ns) among AKIN-1 patients, 26.2% (CI 18.6–35.5, p = 0.006) among AKIN-2 patients [RR 1.77 (1.21–2.58)], and 47.5% (CI 36.9–58.3, p = 0.001) among AKIN-3 patients [RR 3.2 (2.38–4.32)].

Within the lowpr-KD group, the mortality rate for patients without KD was 10.3% (7.38–14.12) (reference group for comparisons), for mild-KD was 12% (6.85–19.96, p = ns), and for severe-KD was 20.6% (14.6–28.19, p = 0.042), with a RR for severe-KD of 2.003 (1.262–3.179).

A logistic regression analysis demonstrated that age, number of antecedents, baseline Crs, Crs at admission, SOFA at admission without renal values and days spent in ICU before the study were related to severe-KD, with a Hosmer-Lemeshow test p = 0.338. A second analysis demonstrated that number of antecedents, days in hospital before ICU, SOFA at admission without renal component and severe-KD were related to mortality, with a Hosmer-Lemeshow test p=0.332 and p=459 respectively (Table 2).

DISCUSSION

The COFRADE study confirms the high prevalence of KD in the ICU, where 42 of 100 patients/day had a CrCl below 60 mL*min^{-1}*1.73 m^{-2}. We demonstrated that over 50% of our patients were subjected to at least 1 potential insult to the kidney . Moreover, awareness of the existence of a kidney injury before admission may have influenced the use of nephrotoxic drugs. Another relevant observation is that among those patients in AKIN-0 stage and low Crs levels, almost 25% of them had in fact a severe dysfunction as measured by CrCl, which was associated with a significant increase in mortality. Our results have potential health implications, demonstrating that the impact of kidney dysfunction in the ICU is greater than has previously been considered and confirming the need for better tools to evaluate kidney function.

Eliminado: mL/(min^{-1}·1.73 m^{-2})

The incidence of AKI in the general population has historically been considered to be low. Liaño et al reported 209 cases per million population in 1996, after applying a rise in Crs over 177 mmol/L as diagnostic criteria (10). More recently, following less restrictive criteria, Ali et al estimated 2147 per million population (11), and Hsu et al doubled that figure to 4085 per million

population (12). However, despite this low incidence, the impact on public health is in fact significant, with over 2 million people expected to die annually of acute kidney injury (13, 14). The situation appears more serious when focusing on hospitalized patients, where incidence ranges from less than 1% in early studies to a wider interval of 3%–20% when applying RIFLE or AKIN criteria and rising even more among patients admitted to the ICU, where incidence, morbi-mortality, and costs increase dramatically.

Until recently, the reported incidence in ICUs was below 10% (15-17). However, with the widespread use of RIFLE (2) and AKIN (3) classifications, incidences have escalated and are estimated between 10%–70% in different studies (18-20). In a recent study analysing AKI in 17 ICUs from Finland, a incidence of 39.3 % was reported, with a estimated population-based incidence of 746 cases per million population per year (21).

Nevertheless the epidemiology of KD in the ICU is not yet complete since, to the best of our knowledge and apart from a study by Hoste et al finding a period-prevalence nearing 70% (6), the COFRADE is the first study that specifically addresses one-day point-prevalence of AKI in this setting. Our results confirm the worst estimates, demonstrating that approximately 60% of our patients exhibit some extent of kidney dysfunction.

Keeping in mind that prevalence studies should not be used to draw conclusions regarding mortality, our results highlight the significance of even mild levels of KD. Mortality increases from 10%, to 16%, and finally to 29% when CrCl drops from 90, to 60–90, and finally below 60 mL*min^{-1}*1.73 m^{-2}, respectively. It is important to note that, in our study, more than 45% of patients with a normal AKIN classification had in fact some degree of kidney dysfunction, and this "undetected" dysfunction conveyed a worse prognosis (22).

Eliminado: mL/(min^{-1}·1.73 m^{-2})

A potential source of error derived from the use of AKIN in this specific study is the possibility that some patients would already have developed AKI before the required 48 hours period for creatinine changes and the episode would be missed. To minimize this source of bias we applied baseline creatinine, an approach now included in the new KDIGO criteria for AKI staging (23) but we must admit that this approach could in some way have influenced the high prevalence in our population by categorizing as AKI some cases that in fact did have kidney dysfunction before admission. We did not try to compute KDIGO criteria because were not proposed when this protocol was designed and this methodology would have introduced new

sources of bias but recent reports have shown similar results for AKI staging when using AKIN or KDIGO criteria (21). Of course, due to the point-prevalence nature of our study we were unable to verify that all of our cases in fact corresponded to an AKI diagnosis (a limitation also present in epidemiologic studies resting in AKIN as diagnostic criteria, since up to two-thirds of patients with AKI present the condition before hospital admission) (21, 24). Even more, we believe that this distinction is not crucial since the same management and preventive measures should apply to any cause of kidney dysfunction, regardless of whether is a developing process (AKI) or was present at admission (13) and in fact Chawla has recently proposed a new model that integrates AKI and chronic kidney disease, considering reduced GFR as a clinical entity that has differential initiation and expression in time (13), a hypothesis that reinforces our approach.

Another potential source of bias of special signification in epidemiological studies is the exclusion of patients. In our study this bias could have been present in some degree considering that excluded cases were mainly cardiac ischemic and showed a better outcome. This selection was unavoidable because the presence of a bladder catheter was necessary to calculate CrCl and less grave cases were excluded from the study. However, the percentage of losses was low (<10%) and should not have interfered in our conclusions.

Other controversial issue addressed by our study is the lack of accurate diagnostic tools. Although Crs is being replaced by the RIFLE and AKIN classifications, which are currently the most widely used, both diagnostic methods have shown inconsistencies in their ability to detect AKI (4, 5, 25). A widely used alternative is estimating CrCl using equations; however, this strategy is not suitable for critically ill patients (26, 27). Therefore, to minimize the risk of underestimating the incidence of AKI, we finally resorted to measuring CrCl (4, 5). Our decision to use diagnostic criteria developed for the chronic patient (9), where CrCl below 60 $mL*min^{-1}*1.73\ m^{-2}$ indicated moderate to severe dysfunction, might be questioned. However, this cut-off value is actually widely used for acute patients.

Eliminado: $mL/(min^{-1}\cdot 1.73\ m^{-2})$

The contribution of drug toxicity in the development of AKI has been estimated at 20%–25% of the most serious cases. On the other hand, the occurrence of kidney dysfunction notably increases the risk for drug-induced nephrotoxicity (28). This is a serious issue since the presence of factors potentially harmful for the kidney, especially nephrotoxic drugs, is high in

the ICU setting. Being ours a prevalence study, we could not explore relationship between drugs usage and kidney dysfunction but tried to put in evidence those patients with kidney dysfunction that were receiving nephrotoxic drugs. Consistently, our results demonstrated that over 50% of patients received at least one potential insult to the kidney. Moreover, a significant number of cases remain unidentified through creatinine or AKIN criteria; therefore, it is highly probable that these patients will be managed without taking into consideration those factors that are potentially harmful for the kidney. This emphasizes the need for highly sensitive methods that could detect even slight reductions in GFR.

One interesting finding was the positive impact that awareness of the presence of dysfunction has on preventive measures, since the occurrence of renal insults (e.g., administration of NSAIDs) was less common among patients with CKD. Therefore, we believe that highlighting the presence of KD in a patient's medical history could contribute to reducing secondary kidney damage. This could be possibly done through computerized clinical reports that signal to professionals and direct their attention to changes in kidney function, as is the procedure followed at our ICU.

Given the absence of effective treatments for AKI, our emphasis currently focuses on prevention strategies, even more now that has been demonstrated that AKI can progress to chronic kidney disease despite the patient having seemingly recovered (29). According to Pannu et al (30), the current preventive strategy could be summarized into 3 main points: (1) identify patients at risk, (2) avoid administering nephrotoxic drugs to them, and (3) re-evaluate kidney function on a regular basis. Our study may be useful in this context since it assesses the impact of KD in the ICU, highlights the insults to which patients are subjected, and demonstrates the feasibility of cyclic prevalence studies in evaluating the results of preventive interventions.

ACKNOWLEDGEMENT

The COFRADE study was endorsed by the Spanish Society of Intensive Care Medicine (SEMICYUC).

INVESTIGATORS OF THE COFRADE STUDY GROUP:

Hospital Clínic. Barcelona:

Servicio de Nefrología: NS Pérez.

ICU hepatology: J Acevedo, A Más, M Castro.

ICU general: JM Nicolás.

ICU surgery: E Zavala (IDIBAPS), R Adalia, FJ Tercero.

ICU nephrology: E Poch, N Serra.

ICU cardiology: X Bosch-Genover.

ICU respiratory: JR Badia.

ICU heart surgery: R Cartana.

ICU anesthesiology: J Fontanals.

Hospital Clínico San Carlos. Madrid.

ICU: F Ortuño-Andériz.

Hospital Costa del Sol. Málaga.

ICU: MI Fernández-García.

Hospital de Alcorcón. Madrid.

ICU: A Núñez-Reiz.

Hospital de Cruces. Bilbao. Osakidetza.

ICU anesthesiology: N Lekerika.

ICU medical: A Sánchez.

Hospital de Guadalajara. Guadalajara.

ICU: C Benito Puncel, JM Borrallo.

Hospital de la Santa Creu i San Pau. Barcelona.

ICU: A Roglán Piqueras, M Rodríguez-López.

Hospital del Norte. Madríd.

ICU: M González-Arenas, M Paloma.

Hospital del Sureste. Madríd.

ICU: M Ochoa-Calero, P Albert-de-la-Cruz, M Cruz-Tejedor.

Hospital del Tajo. Madríd.

ICU: F Ballesteros-Ortega.

Hospital Fundación Jiménez Díaz. Madrid.

ICU: MA Alcalá-Llorente, C Pérez-Calvo, G Oeding-Angulo.

Hospital General Universitario Asociado. Castellón.

ICU: S Mas-Font, R González-Luis, A Ferrándiz-Sellés.

Hospital General Yague. Burgos.

ICU: MJ López-Pueyo, L LLata-Rodríguez, ME Perea Rodríguez.

Hospital Germans Trias i Pujol. Badalona

ICU: TM Tomasa-Irriguible.

Hospital Ramón y Cajal. Madrid.

ICU anesthesiology: A Candela-Toharia.

ICU medical: JA Liétor-Villajos.

Hospital Severo Ochoa. Madríd.

ICU: J López-Martínez, N Chamorro-Borraz, J Suárez-Saiz.

Hospital Torrecárdenas. Almería.

ICU: JA Ramos-Cuadra, A Calderón-Rodríguez, R Rodríguez-Castaño.

Hospital Universitario 12 de Octubre. Madrid.

ICU: JL Flordelis-Lasierra, A Mohedano-Gómez, L Terceros.

ICU (UCP): JL Pérez-Vela.

Hospital Universitario Carlos Haya. Málaga.

ICU: R Lozano-Saez, R Olalla-García, R Aguiar.

Hospital Universitario de Canarias. Tenerife.

ICU: L Lorenzo-de-la-Peña, N Pérez-Martínez.

Hospital Universitario Dr. Peset. Valencia.

ICU: R Zaragoza, E Casanoves-Laparra, Y Montoro-Lozano.

Hospital Universitario Infanta Cristina. Badajoz.

ICU: M Robles-Marcos, R Almaraz-Velarde, MV Trasmonte-Martínez.

Hospital Universitario La Paz. Madrid.

ICU: A Garcia-de-Lorenzo, M Sánchez, E Perales.

Hospital Universitario Puerta del Mar. Cádiz.

ICU: R Sierra-Camerino, AC Sánchez-Rodríguez.

Hospital Vega Baja. Orihuela.

ICU: C Giménez-Esparza-Vich, D Pérez-Martínez, C Portillo-Requena.

Hospital Universitario Virgen de la Arrixaca. Murcia.

ICU: J Ros-Martínez, C Llamas-Lázaro.

Hospital Virgen de la Victoria. Málaga.

ICU: D Daga-Ruiz, J Vidal-Hernández-Rodríguez.

Hospital Virgen de las Nieves. Granada.

ICU traumatology: F Guerrero-López.

Hospital Universitario Virgen de Valme. Sevilla.

ICU: D Herrera-Rojas, A Úbeda-Iglesias, T Contreras-del-Pino.

Hospital Virgen del Rocío. Sevilla.

ICU: R Hinojosa-Pérez.

Hospital Universitario Virgen Macarena. Sevilla

ICU: S Ibáñez-Cuadros, A Arenzana-Seisdedos.

Hospital Xeral. Lugo.

ICU: L Álvarez-Montero, V Nespereira-Jato, O Saornil-Agote.

REFERENCES.

1) Clec'h C, Gonzalez F, Lautrette A, Nguile-Makao M, Garrouste-Orgeas M, Jamali S, et al. Multiple-center evaluation of mortality associated with acute kidney injury in critically ill patients: A competing risks analysis. Crit Care, 2011; 15:R128.

2) Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: The second international consensus conference of the acute dialysis quality initiative (ADQI) group. Crit Care, 2004; 8:R204-12.

3) Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute kidney injury network: Report of an initiative to improve outcomes in acute kidney injury. Crit Care, 2007; 11:R31.

4) Herrera-Gutiérrez ME, Seller-Pérez G, Banderas-Bravo E, Aragón-Gonzalez C, Olalla-Sánchez R, Lozano-Sáez R. Discrepancies in the rifle classification are due to the method used to assess the level of derangement of kidney function. J Crit Care, 2011; 26:572-6.
5) Pickering JW, Frampton CM, Walker RJ, Shaw GM, Endre ZH. Four hour creatinine clearance is better than plasma creatinine for monitoring renal function in critically ill patients. Critical Care, 2012; 16:R107.
6) Hoste EA, Kellum JA. Acute kidney injury: Epidemiology and diagnostic criteria. Curr Opin Crit Care, 2006; 12:531-7.
7) Herrera-Gutiérrez ME, Seller-Pérez G, Maynar-Moliner J, Sánchez-Izquierdo Riera JA, COFRADE-investigators. Variability in renal dysfunction defining criteria and detection methods in intensive care units: Are the international consensus criteria used for diagnosing renal dysfunction? Med Intensiva, 2012; 36:264-70.
8) Herrera-Gutiérrez ME, Seller-Pérez G, Banderas-Bravo E, Muñoz-Bono J, Lebrón-Gallardo M, Fernandez-Ortega JF. Replacement of 24-h creatinine clearance by 2-h creatinine clearance in intensive care unit patients: A single-center study. Intensive Care Med, 2007; 33:1900-6.
9) Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: A position statement from kidney disease: Improving global outcomes (KDIGO). Kidney Int, 2005; 67:2089-100.
10) Liano F, Pascual J. Epidemiology of acute renal failure: A prospective, multicenter, community-based study. Madrid acute renal failure study group. Kidney Int, 1996; 50:811-8.
11) Ali T, Khan I, Simpson W, Prescott G, Townend J, Smith W, et al. Incidence and outcomes in acute kidney injury: A comprehensive population-based study. J Am Soc Nephrol, 2007; 18:1292-8.
12) Hsu CY, McCulloch CE, Fan D, Ordonez JD, Chertow GM, Go AS. Community-based incidence of acute renal failure. Kidney Int, 2007; 72:208-12.
13) Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: An integrated clinical syndrome. Kidney Int, 2012; 82:516-24.
14) Murugan R, Kellum JA. Acute kidney injury: What's the prognosis? Nat Rev Nephrol, 2011; 7:209-17.

15) Brivet FG, Kleinknecht DJ, Loirat P, Landais PJ. Acute renal failure in intensive care units--causes, outcome, and prognostic factors of hospital mortality; a prospective, multicenter study. French study group on acute renal failure. Crit Care Med, 1996; 24:192-8.
16) Herrera-Gutiérrez ME, Seller-Pérez G, Maynar-Moliner J, Sánchez-Izquierdo-Riera JA, FRAMI-investigators. Epidemiology of acute kidney failure in spanish icu. Multicenter prospective study frami. Med Intensiva, 2006; 30:260-7.
17) Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, et al. Acute renal failure in critically ill patients: A multinational, multicenter study. JAMA, 2005; 294:813-8.
18) Thakar CV, Christianson A, Freyberg R, Almenoff P, Render ML. Incidence and outcomes of acute kidney injury in intensive care units: A veterans administration study. Crit Care Med, 2009; 37:2552-8.
19) Bagshaw SM, George C, Bellomo R. A comparison of the rifle and akin criteria for acute kidney injury in critically ill patients. Nephrol Dial Transplant, 2008; 23:1569-74.
20) Ostermann M, Chang RW. Acute kidney injury in the intensive care unit according to rifle. Crit Care Med, 2007; 35:1837-43; quiz 52.
21) Nisula S, Kaukonen KM, Vaara ST, Korhonen AM, Poukkanen M, Karlsson S, et al. Incidence, risk factors and 90-day mortality of patients with acute kidney injury in finnish intensive care units: The finnaki study. Intensive Care Med, 2013; 39:420-8.
22) Hsu CY, Ordonez JD, Chertow GM, Fan D, McCulloch CE, Go AS. The risk of acute renal failure in patients with chronic kidney disease. Kidney Int, 2008; 74:101-7.
23) Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: A KDIGO summary (part 1). Crit Care, 2013; 17:204.
24) Siew ED, Matheny ME, Ikizler TA, Lewis JB, Miller RA, Waitman LR, et al. Commonly used surrogates for baseline renal function affect the classification and prognosis of acute kidney injury. Kidney Int, 2010; 77:536-42.
25) Joannidis M, Metnitz B, Bauer P, Schusterschitz N, Moreno R, Druml W, et al. Acute kidney injury in critically ill patients classified by akin versus rifle using the saps 3 database. Intensive Care Med, 2009; 35:1692-702.
26) Seller-Pérez G, Herrera-Gutiérrez ME, Banderas-Bravo E, Olalla-Sánchez R, Lozano-Sáez R, Quesada-García G. Concordance in critical patients between the equations designed for the

calculation of glomerular filtration rate and 24-hour creatinine clearance. Med Intensiva, 2010; 34:294-302.

27) Hoste EA, Damen J, Vanholder RC, Lameire NH, Delanghe JR, Van den Hauwe K, et al. Assessment of renal function in recently admitted critically ill patients with normal serum creatinine. Nephrol Dial Transplant, 2005; 20:747-53.

28) Perazella M. Drug use and nephrotoxicity in the intensive care unit. Kidney Int, 2012; 81:1172-9.

29) Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term risk of mortality and other adverse outcomes after acute kidney injury: A systematic review and meta-analysis. Am J Kidney Dis, 2009; 53:961-73.

30) Pannu N, Nadim MK. An overview of drug-induced acute kidney injury. Crit Care Med, 2008; 36:S216-23.

Figure E1.

Study flow chart. CKD = Chronic Kidney Disease. CrCl = measured creatinine clearance

Figure 1

Prevalence of kidney dysfunction in the ICU.

Mild dysfunction = creatinine clearance between 90 and 60 mL*min^{-1}*1.73 m^{-2}, severe dysfunction = creatinine clearance below 60 mL*min^{-1}*1.73 m^{-2}. Left bars represent whole population. Right bars represent patients with *low probability of KD* (n=557) defined as absence of previous kidney disease history, serum creatinine below 1.2 gr/dL and AKIN-0 stage.

Legend: Open bar = no dysfunction; Horizontal lines bar = mild dysfunction; Vertical lines bar = severe dysfunction.

Eliminado: mL/min/1.73m^2

Eliminado: mL/min/1.73m^2

Eliminado: Separate full black bar

Eliminado: s

Figure 2

Kidney function measured for each AKIN stage.

Figures over bars = number of cases.

Mild dysfunction = creatinine clearance between 90 and 60 $mL*min^{-1}*1.73\ m^{-2}$, severe dysfunction = creatinine clearance below 60 $mL*min^{-1}*1.73\ m^{-2}$.

Legend: Open bar = No dysfunction; Horizontal lines bar = mild dysfunction; Vertical lines bar = severe dysfunction.

Figure 3

ICU mortality for all cases and separated for different degrees of kidney function.

Mild dysfunction = creatinine clearance between 90 and 60 $mL*min^{-1}*1.73\ m^{-2}$, severe dysfunction = creatinine clearance below 60 $mL*min^{-1}*1.73\ m^{-2}$. Chronic kidney disease (CKD) was compared with no CKD. Mild and severe dysfunctions were compared to no dysfunction.

Legend: Open bar = All cases; Checked bar = Chronic Kidney Disease; Horizontal lines bar = No dysfunction; Vertical lines bar = Mild dysfunction; Black bar = Severe dysfunction.

Eliminado: mL/min/1.73m^2

Eliminado: mL/min/1.73m^2