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# MODÈLE À RISQUES COMPÉTITIFS ET ANALYSE DE PROPENSION APPLIQUÉS À L'ATTEINTE RÉNALE AIGUË EN RÉANIMATION

Christophe Clec'H

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# UNIVERSITÉ DE GRENOBLE

## THÈSE

Pour obtenir le grade de

## DOCTEUR DE L'UNIVERSITÉ DE GRENOBLE

Spécialité : modèles, méthodes et algorithmes en biologie,  
santé et environnement

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l'Environnement

## MODÈLE À RISQUES COMPÉTITIFS ET ANALYSE DE PROPENSION APPLIQUÉS À L'ATTEINTE RÉNALE AIGUË EN RÉANIMATION

Thèse soutenue publiquement le 09 décembre 2010  
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## RESUME

L'atteinte rénale aiguë (ARA) est une pathologie fréquente en réanimation. La littérature actuelle sur le sujet est riche mais globalement hétérogène et confuse. Ainsi, plusieurs questions clés restent à ce jour sans réponse claire. Le but de cette thèse est d'apporter des éléments nouveaux dans le domaine dans un souci de rigueur et d'originalité méthodologiques.

La première partie est consacrée à l'appréciation précise de l'impact pronostique de l'ARA par le modèle à risques compétitifs de Fine et Gray. La deuxième est dédiée à l'évaluation de l'efficacité de l'épuration extra-rénale (EER) par la technique du score de propension. La troisième, enfin, s'intéresse à l'ARA induite par les produits de contraste iodés, cas particulier potentiellement grave mais étonnamment peu étudié jusqu'alors en réanimation.

Les résultats soulignent le pronostic sombre associé à la survenue d'une ARA, l'efficacité incertaine de l'EER et la nécessité urgente d'uniformisation des pratiques en termes de diagnostic et de thérapeutique.

Mots clés : atteinte rénale aiguë, diagnostic, pronostic, épidémiologie, risques compétitifs, score de propension, réanimation.

# COMPETING RISKS MODELING AND PROPENSITY ANALYSIS APPLIED TO THE SETTING OF ACUTE KIDNEY INJURY IN THE INTENSIVE CARE UNIT.

## ABSTRACT

Acute kidney injury (AKI) is commonly encountered in critically ill patients. Although it has been extensively studied so far, many key issues remain unresolved. This aim of this thesis is to bring a new insight in the field through rigorous and original methodological approaches.

In the first part, the prognostic impact of AKI is assessed through the Fine and Gray competing risks model. In the second part, the efficacy of renal replacement therapy (RRT) is evaluated by the propensity score technique. Finally, concerns about contrast-induced AKI, which has been surprisingly under investigated in the intensive care unit, are addressed in the third part.

Results emphasize the poor outcome associated with AKI, cast some doubt on RRT efficacy and stress the need for urgent validation of early and sensitive diagnostic markers, and standardization of AKI management.

Keywords: acute kidney injury, diagnosis, prognosis, epidemiology, competing risks, propensity score, intensive care unit.

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# **Introduction**

L'insuffisance rénale aiguë (IRA) est une situation fréquente en réanimation responsable d'une lourde morbi-mortalité tant immédiate qu'à long terme. Ce constat général ressort d'une littérature globalement hétérogène et confuse dont l'analyse ne permet guère de tirer des conclusions plus précises.<sup>1</sup> Alors que l'IRA touche une proportion substantielle de patients et a fait l'objet de nombreuses études, il existe paradoxalement plus d'interrogations et de zones d'ombre que de certitudes, aussi bien sur le plan épidémiologique que sur le plan thérapeutique.

Deux raisons, principalement, expliquent cet état de faits. La première raison tient à la difficulté de caractériser la notion même d'IRA comme en témoigne la multiplicité des définitions retenues par les différents auteurs.<sup>2</sup> Si tous ont de l'IRA une conception physiopathologique unique, les avis concernant les meilleurs marqueurs diagnostiques et les seuils appropriés sont franchement divergents. Ainsi, en fonction de la définition utilisée, l'incidence et la mortalité varient considérablement. La deuxième raison, quant à elle, tient à l'absence de recommandations claires pour la prise en charge de l'IRA liée au faible niveau de preuve des études disponibles à ce jour. Ceci s'applique particulièrement à l'épuration extra-rénale (EER), un des piliers du traitement, dont les indications, les modalités optimales et l'efficacité réelle restent très incertaines.<sup>1,3</sup>

La littérature actuelle dans le domaine de l'IRA se caractérise ainsi par une grande hétérogénéité qui d'une part rend difficile l'interprétation des résultats et la comparaison des études, et d'autre part met en évidence la nécessité d'entreprendre des investigations complémentaires afin de répondre aux questions en suspens. Par ailleurs, il faut souligner les carences méthodologiques de bon nombre d'études dans lesquelles les multiples facteurs de confusion sont ignorés et les modèles statistiques utilisés inadaptés.

Le but de cette thèse est d'apporter des éléments nouveaux dans les champs épidémiologique et thérapeutique de l'IRA dans un souci de rigueur et d'originalité méthodologiques.



La première partie sera consacrée à l'évaluation de l'incidence de l'IRA et de son impact sur la mortalité dans une population générale de réanimation. L'IRA sera définie selon des critères diagnostiques récents présentés comme consensuels, les critères RIFLE,<sup>4</sup> et l'analyse de survie fera appel à un modèle multi-états à risques compétitifs, le modèle de Fine et Gray.<sup>5</sup> La deuxième partie sera dédiée à la place de l'EER dans le traitement de l'IRA. Après appariement de patients avec IRA épurés et non épurés sur un score de propension dont on exposera la théorie et la construction, le lien entre EER et survie en réanimation sera estimé par un modèle de régression logistique conditionnelle.

La troisième partie sera centrée sur un cas particulier potentiellement fréquent et grave en réanimation mais étonnamment peu exploré jusqu'alors : l'IRA induite par les produits de contraste iodés.<sup>6, 7</sup> Son impact sur la mortalité sera évalué par un modèle de régression logistique. Les termes du débat opposant les partisans de ce modèle classique à ceux des modèles de survie (modèle de Cox et modèles à risques compétitifs) seront exposés.

Chaque partie sera présentée sous la forme d'une introduction épidémiologique au problème soulevé suivie de considérations méthodologiques spécifiques et de l'article qui en constitue le développement.

On conclura par la synthèse des résultats et l'évocation des futurs axes de recherche.

# **Première partie**

*Impact pronostique*

## I.1 Considérations épidémiologiques

L'IRA se caractérise par un déclin rapide de la fonction des néphrons, se développant sur quelques heures à quelques jours, responsable de perturbations hydro-électrolytiques et acido-basiques plus ou moins marquées avec perte consécutive de l'homéostasie. Simple et unanimement admise sur le plan conceptuel, la notion d'IRA est longtemps restée imprécise sur le plan opérationnel.

Ainsi, avant 2004 et la proposition de critères diagnostiques consensuels que nous détaillerons plus loin dans ce chapitre, plus de 35 définitions d'IRA ont été recensées dans la littérature : certaines basées sur le critère créatininémie, avec des différences substantielles en termes de seuil et de variation absolue ou relative ; d'autres sur le critère diurèse, avec également d'importantes variations de seuil ; d'autres encore sur la nécessité de recourir à l'épuration extra-rénale (EER), sans que l'indication exacte n'en soit pour autant précisée.<sup>2</sup>

En fonction de la définition retenue, l'incidence et la mortalité varient dans de larges proportions, de 1 à 25% et de 15 à 60%, respectivement.<sup>5, 7, 8-15</sup> Au-delà de ce problème de définition, la grande majorité des études ne fournit que des chiffres de mortalité brute et ne permet donc pas de savoir si les patients meurent d'IRA ou avec une IRA, en d'autres termes si l'IRA est en soi un facteur de risque de mortalité ou reflète simplement la gravité globale des patients. Une seule étude, largement citée, a tenté de trancher la question. Il s'agit de celle de Metnitz et al., publiée en 2002 dans *Critical Care Medicine*.<sup>16</sup> La conclusion était que l'IRA était un facteur indépendant de mortalité en réanimation conduisant à la publication simultanée d'un éditorial intitulé « Les patients meurent d'insuffisance rénale aiguë ».<sup>17</sup> Cette étude, intéressante de par son objectif et son caractère multicentrique, présente toutefois de multiples écueils dont les deux principaux sont la sélection de patients requérant la mise sous EER, sur des critères non définis qui plus est, et la non prise en compte manifeste de

l'appariement des patients dans l'analyse statistique. De ce fait les résultats auraient dû être interprétés avec plus de prudence et la conclusion de l'éditorial associé paraît quelque peu hâtive.

L'absence de définition consensuelle représentant un obstacle majeur à la recherche épidémiologique dans le domaine de l'IRA, des experts en néphrologie et en réanimation se regroupèrent au sein du groupe ADQI (Acute Dialysis Quality Initiative) et développèrent une nouvelle classification publiée en 2004 comportant trois stades de gravité croissante, R pour « risk », I pour « injury » et F pour « failure », ainsi que deux stades pronostiques, L pour « loss » (perte de la fonction rénale pendant plus de quatre semaines) et E pour « end-stage kidney disease » (perte de la fonction rénale pendant plus de trois mois).<sup>4</sup> Cette classification RIFLE propose d'adopter comme définition « universelle » de l'IRA soit un critère de débit de filtration glomérulaire (DFG), reflété par l'augmentation relative de la créatininémie par rapport à la valeur basale observée ou calculée à partir de la formule MDRD (Modification of Diet in Renal Disease), soit un critère de diurèse, le stade de gravité de l'IRA étant déterminé par le plus altéré de ces deux critères :

Classe RIFLE	Critère de DFG	Critère de diurèse
Risk	Augmentation de la créatininémie ≥ 1.5 X valeur de base ou diminution du DFG ≥ 25 %	< 0.5 ml/kg/h pendant ≥ 6 h
Injury	Augmentation de la créatininémie ≥ 2 X valeur de base ou diminution du DFG ≥ 50 %	< 0.5 ml/kg/h pendant ≥ 12 h
Failure	Augmentation de la créatininémie ≥ 3 X valeur de base ou diminution du DFG ≥ 75 % ou créatininémie ≥ 350 µmol/L avec augmentation aiguë ≥ 44 µmol/L	< 0.3 ml/kg/h pendant ≥ 24 h ou anurie ≥ 12 h

Outre cette définition universelle, le groupe ADQI proposa un changement de nomenclature afin de refléter plus précisément le continuum nosologique allant de la dysfonction rénale modérée à l'atteinte sévère terminale qu'est en fait l'IRA. Ainsi, le terme acute kidney injury (AKI), que l'on peut traduire par atteinte rénale aiguë, a remplacé celui d'IRA. Dans un souci de clarté et de précision, il en sera fait de même ici et l'acronyme anglo-saxon sera donc utilisé préférentiellement dans la suite du texte.

En 2007, le groupe AKIN (Acute Kidney Injury Network), composé en partie des mêmes membres que le groupe ADQI, proposa une nouvelle classification, ou plus exactement un ajustement de la classification précédente, les stades 1, 2 et 3 de la classification AKIN correspondant à peu de différences près aux stades R, I et F de la classification RIFLE.<sup>18</sup> Les principales modifications apportées par la classification AKIN sont les suivantes : une augmentation modérée de créatininémie ( $> 26.2 \mu\text{mol/L}$ ) marquant le début de l'AKI, un délai de 48 heures définissant le caractère aigu de l'atteinte et, enfin, le recours à l'EER imposant un classement des patients en stade 3 (le plus sévère). En dehors du caractère très discuté de cette dernière modification, la classification AKIN ne semble pas plus performante, voire moins, que la classification RIFLE que nous avons donc choisi de continuer à utiliser.<sup>19-21</sup>

Depuis sa publication, la classification RIFLE a fait l'objet d'évaluations dans des contextes variés. En réanimation, seules trois études multicentriques ont été conduites,<sup>22-24</sup> en dehors de celle de Maccariello et al.<sup>25</sup> portant sur des malades épurés uniquement. Leurs conclusions sont concordantes même s'il existe des différences notables en terme d'incidence et de mortalité brute, soulignant bien que la classification RIFLE n'a probablement pas résolu tous les problèmes de caractérisation de l'épidémiologie de l'AKI. En revanche, l'association entre AKI et mortalité y est estimée par des modèles multivariés, ce qui constitue un avantage considérable par rapport aux études antérieures, à cette réserve près que les modèles en

question ne sont peut-être plus les mieux adaptés à l'analyse de survie comme cela est discuté dans le chapitre qui suit.

## I.2 Considérations méthodologiques

Dans les études citées ci-dessus, l'association entre survenue d'une AKI et mortalité est estimée soit par un modèle de régression logistique,<sup>22, 24</sup> soit par un modèle de Cox.<sup>23</sup> Or la pertinence de ces modèles est contestée par certains auteurs.<sup>26, 27</sup> Pour comprendre leur position, quelques notions sur la théorie des modèles sont nécessaires.

La régression logistique est certainement le modèle le plus utilisé en réanimation lorsqu'il s'agit de rechercher des facteurs de risque indépendants de mortalité. Il s'écrit de la façon suivante :

$$\text{Logit } P_i = \alpha + \beta_1 X_{i1} + \beta_2 X_{i2} + \dots + \beta_k X_{ik}$$

où  $P_i$  est la probabilité de décès et  $\text{logit de } P_i$  le log de  $(P_i/1-P_i)$ , avec  $i = 1, 2, \dots, n$  individus.

La probabilité de décès est la variable à expliquer (ou variable dépendante) que l'on cherche à rattacher à un certain nombre de variables explicatives (ou variables indépendantes) que sont les  $k$   $X_i$ . Les paramètres  $\beta$ , quant à eux, sont les coefficients de régression obtenus par la méthode du maximum de vraisemblance. La relation entre chacune des variables explicatives et la variable à expliquer est exprimée sous forme d'odds ratio (OR), avec  $OR = \exp(\beta)$ . L'intercepte  $\alpha$ , qui serait égal au  $\text{logit de } P_i$  dans le cas non pertinent où toutes les variables explicatives vaudraient zéro, n'a lui pas d'interprétation « clinique » directe.

Les défauts majeurs du modèle de régression logistique sont :

- *la non prise en compte du délai de survenue de l'événement d'intérêt* (le décès dans le cas qui nous intéresse, mais il peut s'agir de n'importe quelle variable qualitative binaire), alors que la durée de séjour en réanimation peut être en soi un facteur de risque de mortalité,

- *l'absence de prise en compte de la censure droite* (un individu est dit censuré s'il n'a pas présenté l'événement d'intérêt à la fin de sa période d'observation qui peut correspondre soit à la date effective de fin de l'étude soit à une date antérieure s'il est perdu de vue avant la fin de l'étude) : le temps de suivi est donc supposé constant pour tous les individus, ce qui est problématique car il varie en fait largement et les variations de temps de suivi entre des groupes d'exposition différente peut conduire à des estimations erronées de l'impact de l'exposition, et
- *l'absence de prise en compte du caractère dépendant du temps des variables explicatives* pouvant conduire là encore à une estimation biaisée de la force de l'association entre ce facteur de risque et la mortalité. Par exemple, un individu présentant un facteur de risque spécifique de mortalité au 10<sup>ème</sup> jour de réanimation est considéré dans ce modèle comme étant exposé au risque tout au long de son séjour.

Le modèle à risques proportionnels présenté par DR. Cox en 1972 pallie en grande partie les inconvénients de la régression logistique.<sup>28</sup> Il s'écrit de la façon suivante :

$$h(t|X_i) = h_0(t) \exp \{ \beta_1 X_{i1} + \dots + \beta_k X_{ik} \} ,$$

avec  $i = 1, 2, \dots, n$  individus et  $k$  variables explicatives  $X_i$

Dans ce modèle, le risque de décès d'un individu à un instant  $t$ ,  $h_i(t)$ , dépend d'un risque de base,  $\lambda_0(t)$ , et de l'exponentielle d'un vecteur de covariables explicatives. La force de l'association entre un facteur de risque  $X$  et la mortalité est exprimée sous forme de hazard ratio (HR), avec :

$$HR = h(t|X_i) / h(t|X_j) = \exp \{ \beta^t (X_i - X_j) \}$$



Ainsi, le risque de décès d'un individu  $i$ , à chaque instant  $t$ , est une proportion fixe du risque d'un individu  $j$ . Notons par ailleurs que OR et HR qui représentent tous deux la force de l'association entre un facteur de risque  $X$  et la mortalité ne s'interprètent pas de la même façon. En effet, alors que l'OR s'apparente à une mortalité cumulée, le HR est plutôt une fonction de risque instantané de décès.

Par rapport à la régression logistique, le modèle de Cox présente les avantages suivants :

- *le caractère dynamique de l'événement d'intérêt* qui n'est plus considéré comme simplement binaire,
- *la prise en compte de la notion de variations de durée de suivi entre les individus et donc de la censure droite* qui est en soi porteuse d'information (si le délai de survenue de l'événement d'intérêt n'est pas connu pour certains individus, on sait en revanche qu'il serait toujours plus long que la période d'observation), et
- *la possibilité d'introduire des covariables dépendantes du temps*, permettant une estimation de l'impact de l'exposition réelle à un facteur de risque.

Pour autant, le modèle de Cox n'est pas idéal. Son défaut principal est de faire l'hypothèse que la censure à droite est non informative. En d'autres termes, le temps de survie est supposé indépendant de la censure, ce qui implique que les patients censurés à un instant  $t$  soient représentatifs de tous les patients non censurés à cet instant  $t$  et n'ayant pas présenté l'événement d'intérêt. Cette hypothèse se vérifie probablement lorsque la date de censure est prédéfinie, c'est-à-dire lorsque le suivi s'arrête à la même date fixée antérieurement au début de l'étude pour l'ensemble des individus d'une cohorte. En revanche, elle est peu plausible si la censure dépend d'un changement d'état de santé des individus. Par exemple, les patients

sortent vivants de réanimation ou de l'hôpital (sont censurés) à un instant  $t$  soit parce que leur état s'est amélioré soit, au contraire, parce qu'ils sont au-delà de toute ressource thérapeutique et ne relèvent plus que de soins palliatifs. Ces patients présentent donc un risque de mortalité plus faible, ou plus élevé, que les autres patients maintenus en réanimation ou à l'hôpital (non censurés) à cet instant  $t$  et l'hypothèse de censure non informative est clairement prise en défaut. De plus, la sortie vivant de réanimation ou de l'hôpital empêche nécessairement d'observer un éventuel décès qui ne peut plus survenir comme événement premier. Cette situation définit la notion de risques compétitifs. Typiquement, « sortie » et « décès » sont deux risques compétitifs en ce sens qu'ils constituent deux événements mutuellement exclusifs. Ainsi, lorsque la mortalité en réanimation, ou la mortalité hospitalière, est l'événement d'intérêt, la censure est informative et les méthodes classiques d'analyse de survie telles que le modèle de Cox ne sont plus forcément valides. Des méthodes spécifiques peuvent alors se révéler nécessaires.

Le modèle de Fine et Gray, publié en 1999,<sup>5</sup> a été développé dans cet esprit. Il s'agit d'une extension du modèle de Cox adaptée à l'identification de facteurs pronostiques dans un contexte de risques compétitifs. Dans le modèle de Cox, les patients censurés (sortis vivants) ne sont plus considérés comme susceptibles de présenter l'événement d'intérêt (le décès) et sortent de l'échantillon des patients à risque. Dans le modèle de Fine et Gray, au contraire, les patients censurés sont toujours considérés comme susceptibles de présenter l'événement d'intérêt et sont maintenus dans l'échantillon des patients à risque. De la sorte, restent dans l'échantillon à risque à un instant  $t$  seuls les patients qui n'ont encore présenté aucun événement dans le modèle de Cox et tous les patients qui n'ont pas encore présenté l'événement d'intérêt dans le modèle de Fine et Gray, ce qui inclut par conséquent aussi ceux qui ont présenté l'événement en compétition (la sortie vivant) avant  $t$ . Malgré son caractère assez peu intuitif et naturel, ce procédé apparaît tout à fait valide sur le plan statistique.<sup>5</sup> Par

ailleurs, comme l'hypothèse de censure non informative (ou d'indépendance de l'événement d'intérêt par rapport à la censure) n'est pas respectée, la probabilité de l'événement d'intérêt dans le modèle de Fine et Gray est estimée non pas par la méthode de Kaplan-Meier devenue inappropriée mais par la fonction d'incidence cumulée (FIC) qui a été décrite comme l'outil le plus performant dans ce cas.<sup>29</sup> Contrairement à la fonction de distribution qui tend vers 1, la FIC tend elle vers la proportion globale de décès. Aussi la nomme-t-on également fonction de sous-distribution. La force de l'association entre chaque facteur pronostique et l'événement d'intérêt (le décès) dans ce modèle est exprimée sous la forme de sub-hazard ratio (SHR) qui correspond au ratio des risques associés à la FIC en la présence et en l'absence du facteur pronostique. De ce fait, le modèle de Fine et Gray prédit l'incidence cumulée de décès qui tend vers la prévalence de décès. Notons qu'à l'origine, ce modèle a été conçu pour des variables indépendantes du temps mais qu'il permet malgré tout la gestion de variables temps-dépendantes (qui ne deviennent fixes qu'à partir de la survenue du premier événement en compétition). Les incidences cumulées ne sont alors plus disponibles mais l'on peut toujours considérer les risques cumulés et calculer ainsi les SHR.<sup>30</sup>

Pour clore ce chapitre, il faut souligner que le modèle de Cox « cause-specific » permet également l'analyse des risques compétitifs mais qu'il semble davantage adapté à la modélisation du risque instantané de l'événement d'intérêt (par exemple, la survenue d'une infection nosocomiale).<sup>31</sup> Lorsqu'il s'agit de modéliser la prévalence de l'événement d'intérêt (par exemple, la mortalité en réanimation ou la mortalité hospitalière), le modèle de Fine et Gray est en théorie préférable.

Un exemple d'application du modèle de Fine et Gray est donné dans le chapitre suivant.

### **I.3 Application**

Cet article se propose d'évaluer l'impact pronostique de l'AKI, définie suivant les critères RIFLE, par le modèle à risques compétitifs de Fine et Gray. Il a été soumis pour publication à « *Critical Care Medicine* ».

Il constitue l'une des rares évaluations multicentriques de la classification RIFLE en réanimation. Il confirme non seulement sa validité externe mais fournit également, grâce à l'utilisation d'un modèle statistique plus élaboré que la régression logistique ou le modèle de Cox, une estimation probablement plus juste de l'association entre AKI et mortalité que celles proposées antérieurement.

**Impact of acute kidney injury on intensive care unit patients' outcome: an original  
multi-state, competing risks approach.**

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No reprints will be ordered.

Key words: acute kidney injury, intensive care unit, prognosis, multistate model, competing risks, Fine and Gray.

## **Abstract**

**Objectives:** To assess the prognosis of acute kidney injury (AKI) defined by recent consensus criteria (RIFLE) through an original multi-state, competing risks approach (Fine and Gray model).

**Design:** Observational, multiple-center cohort study.

**Setting:** Thirteen French medical or surgical intensive care units (ICUs).

**Patients:** Unselected patients with ICU stays  $\geq 24$  hrs admitted between 1997 and 2009.

**Interventions:** None.

**Measurements and main results:** The following data were recorded: baseline characteristics, daily serum creatinine, daily Sequential Organ Failure Assessment (SOFA) score, vital status at ICU and hospital discharge, and lengths of ICU and hospital stays. Of the 8639 study patients, 32.9% had AKI, of whom 19.1% received RRT. Patients with AKI had higher crude mortality rates and longer lengths of ICU and hospital stays than patients without AKI. In the Fine and Gray model, independent risk factors for ICU mortality were: RIFLE classes Injury (sub-hazard ratio -SHR-: 2.80; 95% confidence interval -CI-: 2.33-3.36;  $p < 0.0001$ ) and Failure (SHR: 2.46; 95% CI: 2.04-2.95;  $p < 0.0001$ ), Simplified Acute Physiology Score II (SHR: 1.056 per point; 95% CI: 1.053-1.059;  $p < 0.0001$ ), class 3 of McCabe (SHR: 1.82; 95% CI: 1.53-2.17-3.02;  $p < 0.0001$ ), and respiratory failure defined according to the SOFA score (SHR: 3.22; 95% CI: 1.27-8.13;  $p = 0.01$ ). Similar results were found for hospital mortality. Risk class of RIFLE was associated with a trend towards increased hospital mortality.

**Conclusions:** AKI was an overall predictor of poor outcome and mortality differed according to the maximum RIFLE class reached during the ICU stay.

## INTRODUCTION

Acute renal failure (ARF) is as an abrupt decline in kidney function. Although simple to define conceptually, there has long been no consensus on an operational definition of ARF. As reported in a recent survey, more than 35 definitions have been used in literature (1). Some were based on changes in serum creatinine levels with high variability in the relative or absolute magnitude of change, others on the presence of oliguria, and still others on the need for renal replacement therapy (RRT). Depending on the definitions used, ARF has been shown to affect from 1% to 25% of intensive care unit (ICU) patients and has led to mortality rates from 15% to 60% (2-9).

The lack of a uniform definition being a major impediment to epidemiological research in the field, the Acute Dialysis Quality Initiative (ADQI) Group recently proposed consensus definition criteria (10), namely the RIFLE criteria, based on three grades of increasing severity (Risk of renal dysfunction, Injury to the kidney, and Failure of kidney function) and two outcome classes (Loss of kidney function, and End-stage kidney disease), (table 1). Furthermore, the term acute kidney injury (AKI) has replaced the old nomenclature ARF to encompass the entire spectrum of the syndrome, from minor changes in renal function to need for RRT.

The RIFLE classification is undoubtedly a major advance. Since its publication, it has been used in a variety of settings. Overall, RIFLE criteria correlate well with patients' outcome (11-14). In the intensive care unit (ICU) setting, single-center studies showed that mortality increased with increasing RIFLE class (15-17), and all multiple-center studies but one reported consistent results (16, 18-20). Only the study of Maccariello et al., that was performed on selected patients requiring RRT, found no association between RIFLE class and outcome (19).



According to these recent data, AKI seems to be associated with a two to three-fold increase in mortality. However, whether these estimations are unbiased is questionable. Actually, the above mentioned studies used traditional statistical approaches such as the logistic regression model or the Cox model, although these models may not be the most appropriate ones (21). Briefly, the standard logistic regression ignores the timing of events and their chronological order, potentially leading to an overestimation of the association between a specific risk factor (e.g. nosocomial pneumonia) and mortality (22). This problem can be solved to some extent by applying the Cox model, which allows considering time-dependent covariates. Yet, this model does not deal with the competing risks issue. This issue arises when more than one endpoint is possible (23). Typically, “dying in ICU or in hospital” and “discharge alive” are two competing risks. If “dying in ICU or in hospital” is the event of interest, the non-fatal competing event “discharge alive” hinders the event of interest from occurring as a first event.

Statistical models able to handle time-dependent covariates (multistate model) and simultaneously analyze different endpoints (i.e., competing risks) are now available (22, 24-26). In recent years, they have gained growing interest in hospital epidemiology (especially in cancer research) but have been rarely used in the ICU field.

The aim of this study was to assess the association of AKI with ICU patients’ outcome using such an original multistate, competing risks approach.

## **MATERIALS AND METHODS**

### *Study Design and Data Source*

We conducted an observational study in a multiple-center database (OUTCOMEREA) from January 1997 to June 2009. The database, which receives information from 13 French

ICUs, is designed to record daily disease severity scores and the occurrence of iatrogenic events. Methods of data collection and quality of the database have been described in details elsewhere (27). Briefly a large set of data on a random sample of patients older than 16 years with ICU stays longer than 24 h was prospectively collected by the senior physicians of the participating ICUs and entered into the database each year. Participating ICUs could choose between two sampling methods: consecutive admitted patients in randomized beds or consecutive admitted patients in a randomized month. The quality control procedure involved multiple automatic checking of internal consistency and biennial audits. Moreover, a one-day data-capture training course is held once a year for all OutcomeRea investigators and study monitors. Senior physicians and participating centers are listed in the appendix.

In accordance with French law, the OUTCOMEREA database was declared to the Commission Nationale de l'Informatique et des Libertés. The study was approved by the ethics committee of Clermont-Ferrand, France. Because routine collection of data entered into the database did not modify patients' management in any way, and statistical analyses were processed anonymously, informed consent for participation in the study was waived.

### *Study Population and definitions*

All patients in the database were eligible. Exclusion criteria were: history of chronic kidney disease (with or without complete loss of kidney function) assessed according to the Acute Physiology and Chronic Health Evaluation (APACHE) II definitions (28), non-organic (pre-renal) cause of renal dysfunction, decision to withhold or withdraw life-sustaining treatments, and RRT for extra-renal indications (e.g., intoxications or cardiogenic shock).

Patients were classified according to the maximum RIFLE class (no AKI, Risk, Injury or Failure) reached during their ICU stay, as in previous reports (16, 18, 20). Since the 6- and 12-hrs urine outputs were not recorded in the database, we used the glomerular filtration rate

(GFR) only. The GFR criteria were determined according to changes in serum creatinine from baseline values. Because AKI may be present on ICU admission in a high proportion of patients, we chose to assess baseline creatinine values using the Modification of Diet in Renal Disease (MDRD) equation. As recommended by the Acute Dialysis Quality Initiative Group, a normal GFR of 75 ml/min/1.73 m<sup>2</sup> before ICU admission was assumed (10).

For patients who were admitted more than once to the ICU, only the first ICU stay was included in the analysis.

### *Data Collection*

The following data were recorded:

- on ICU admission: age, sex, Mc Cabe class (class 1, no fatal underlying disease; class 2, underlying disease fatal within 5 years; class 3, underlying disease fatal within 1 year), Simplified Acute Physiology Score (SAPS) II, comorbidities assessed according to the Acute Physiology and Chronic Health Evaluation (APACHE) II definitions, transfer from ward (defined as a stay in an acute-bed ward  $\geq$  24 hrs immediately before ICU admission), and admission category (medical, scheduled surgery, or unscheduled surgery),
- during the ICU stay: daily serum creatinine, time from admission to occurrence of AKI, time from admission to the maximum RIFLE class, daily Sequential Organ Failure Assessment (SOFA) score, and occurrence of sepsis,
- on ICU discharge: renal status (recovery or need for prolonged renal support), length of ICU stay, and vital status,
- on hospital discharge: length of hospital stay, and vital status.

### *Endpoints*

The primary endpoints were ICU and hospital mortality.

The secondary endpoints were lengths of ICU and hospital stays, and renal status on ICU discharge.

### *Statistical Analyses*

Comparisons of patients with and those without AKI were based on chi-square tests for categorical data, and on Student's t-test or Wilcoxon's test for continuous data, as appropriate. Comparisons of AKI patients according to their maximum RIFLE class were based on chi-square tests for categorical data, and on one-way analysis of variance (ANOVA) or Kruskal-Wallis' test for continuous data, as appropriate.

The association of AKI with mortality was assessed through the Fine and Gray subdistribution hazard regression model (29), which extends the Cox model to competing risk data by considering the hazard function associated with the cumulative incidence function (CIF). The main advantage of the CIF and Fine and Gray model over the Kaplan-Meier (KM) method and Cox model pertains to censoring. Indeed the KM method and Cox model assume that censoring is non-informative (ie, that the survival time of an individual is independent of censoring). Accordingly, patients discharged alive at time  $t$  are considered as representative of all other patients who have survived to this time  $t$  but who have still not been discharged. This may be true when the censoring process operates randomly. However, this assumption can probably not be made in the case of ICU patients. Actually, since these patients are discharged alive (censored) because of an improvement (or sometimes a deterioration) of their medical state, they have a lower (or sometimes higher) risk of dying than the average, and are therefore not representative of other patients who have not been censored yet. Thus, censoring is clearly informative (ie, the survival time of an individual does depend on censoring). In other words, informative censoring defines a competing risk, given that discharge alive affects

the probability of experiencing the event of interest (death before discharge). In this setting, standard survival methods are no longer valid and specific approaches, such as the CIF and Fine and Gray model that allow handling of both time to events and informative censoring (30, 31), merit consideration.

At time  $t$ , the CIF defines the probability of dying, provided that the study population has survived on time  $t-1$ . Contrarily to a distribution function that tends to 1, the CIF tends to the raw proportion of deaths. So, it is also called “subdistribution function”. The strength of the association between a specific risk factor and the event of interest in the Fine and Gray model is reflected by the sub-hazard ratio (SHR), which is the ratio of hazards associated with the CIF in the presence of and in the absence of the risk factor. Note that this model was originally developed for time-independent risk factors (29). However, while cumulative incidences are not available anymore for time-dependent risk factors, cumulative hazards may be considered instead and SHR can still be computed (32).

We first computed SHR for mortality and 95% confidence intervals (CI) associated with each of the Risk, Injury and Failure classes in univariate analysis. Then, we performed a multivariate analysis to adjust for the following pre-defined potential confounding factors: baseline characteristics (SAPS II, Mc Cabe class, admission category, transfer from ward), and other organ failures (assessed by a specific SOFA component  $> 2$ ) occurring before AKI. Each RIFLE class, and organ failures were entered into the Fine and Gray model as time-dependent variables to account for their timing and chronological order (32).

A  $p$  value less than .05 was considered significant. Analyses were computed using the SAS 9.1 (SAS Institute, Cary, NC, USA) and the free R software packages.

## **RESULTS**

### *Study population*

Of the 10911 patients in the OUTCOMEREA database, 2272 (20.8 %) had exclusion criteria.

Among the remaining 8639 patients, 2846 (32.9 %) had AKI, of whom 545 (19.1 %) received RRT (figure 1).

Patients with AKI were older, had higher severity scores, were more likely to have undergone unscheduled surgery, and had more severe comorbidities than patients without AKI. The demographic and clinical characteristics of patients with and without AKI are shown in table 2.

Among AKI patients, higher severity scores, and unscheduled surgery were associated with a higher degree of renal dysfunction. The demographic and clinical characteristics of AKI patients according to the maximum RIFLE class reached during the ICU stay are shown in table 3.

### *Dynamics of AKI*

AKI was a rapidly evolving process. Times from ICU admission to occurrence of AKI (median in days, [interquartile range]) were 1 [1-2], 2 [1-2], and 1 [1-2] in R, I, and F patients, respectively. Times from ICU admission to maximum RIFLE class were 1 [1-2], 2 [1-3], and 2 [1-3] in R, I, and F patients, respectively.

Some patients displayed a progression of their renal dysfunction despite RRT.

Figure 2 illustrates the dynamics of AKI in our cohort of patients.

### *Impact of AKI on mortality*

Overall, mortality rates were higher in patients with than in those without AKI (ICU mortality: 21.4 % vs 5.7 %,  $p < 0.0001$ ; hospital mortality: 27.6 % vs 8.7 %,  $p < 0.0001$ ).

Among AKI patients, I and F classes were associated with higher mortality rates than R class (ICU mortality: 27.6 % and 26.3 % vs 11.7 %,  $p < 0.0001$ ; hospital mortality: 33.9 % and 33.5 % vs 16.7 %,  $p < 0.0001$ ).

The Fine and Gray model revealed that I and F classes, but not R class, were independent risk factors for ICU and hospital mortality (table 4). Other variables independently associated with mortality were: SAPS II score, class 3 of McCabe, and respiratory failure occurring before AKI onset (table 4).

#### *Impact of AKI on lengths of stays and need for prolonged renal support*

Lengths of ICU and hospital stays were longer in patients with than in those without AKI (table 5).

On ICU discharge, 92/2846 (3.2 %) patients still needed renal support. In each RIFLE class, patients who received RRT had higher SAPS II scores and higher mortality rates than those who did not receive RRT (table 6).

## **DISCUSSION**

The association of AKI with critically ill patients' outcomes has been widely investigated but very few multiple-center evaluations using the RIFLE criteria have been published so far (16, 18-20). Our study carried out on a large cohort of general ICU patients supports the use of RIFLE as a classification tool and adds strong evidence that AKI negatively influences patients' outcome.

The originality of our results mainly lies in the multistate, competing risks approach. This approach has many advantages over the commonly used logistic regression and Cox models. Actually, logistic regression has been reported to cause loss of information because it yields a time-independent probability of dying and ignores the timing of event and their

chronological order (33, 34). While the Cox model may partially alleviate these limits, it has been shown to overestimate the incidence of the event of interest, most of the overestimation being related to the rate of the competing event (35). By contrast, the Fine and Gray model adequately addresses time spent in the ICU (hospital) as a risk factor for ICU (hospital) mortality by considering death hazard rates, and takes into account the time-varying exposure status, thus avoiding a potential misjudgment in terms of time-dependent bias (36, 37). Moreover it provides a more accurate estimation of mortality since death hazard rates are not confounded by the competing event “discharge alive”.

In keeping with the few available similar studies (16, 18, 20), we found that AKI was an overall predictor of poor outcomes, and that mortality differed according to the maximum RIFLE class reached during the ICU stay. However, by applying an original multi-state competing risks approach, we not only confirmed previous results but we also provided a refined estimation of the association between AKI and mortality.

Among R class patients, we showed no association with ICU mortality and a trend towards an increased risk of hospital mortality. Although a similar finding has already been reported by Hoste et al. (16), a more likely explanation is a potential lack of power. Actually, even a moderate renal dysfunction seems to impair patients’ prognosis (18, 20, 38).

On the other hand, I and F classes were independently associated with increased ICU and hospital mortality, with interestingly similar sub-hazard ratios in both classes. These data suggest, like in the study of Ostermann et al. (20), that the maximum risk of death might be reached as soon as patients are on I class. Thus, therapeutic and preventive strategies, such as optimization of hemodynamic parameters and avoidance of nephrotoxic drugs, must undoubtedly be in order at an early stage of renal dysfunction to prevent further aggravation and reduce the risk of death. Whether RRT should also be started early remains an unresolved question. In our cohort, RRT seemed to be all the more effective, as the degree of renal



dysfunction was high. It prevented aggravation in only a low proportion of patients with an initial moderate renal dysfunction but may have protected F patients from death, as suggested by the fact that F patients were more likely to be put on RRT and had a slightly lower risk of death than I patients. Nevertheless, our data do not allow any conclusion as to the impact of RRT. The potential benefit of RRT and the optimal level at which RRT should be initiated are two important issues that need further investigation.

Despite its strengths, our study has some limits that merit consideration.

First, the definition of AKI was not based on the most recent consensus criteria proposed by the AKIN group (39). The main differences between AKIN and RIFLE classifications are as follows: a smaller change in serum creatinine ( $> 26.2 \mu\text{mol/L}$ ) used to identify patients with stage 1 AKI (analogous to RIFLE-Risk), a time constraint of 48 hrs for the diagnosis of AKI, and any patient receiving RRT classified as stage 3 AKI. However, compared to RIFLE criteria, there is currently no evidence that AKIN criteria improve the sensitivity, robustness and predictive ability of the definition and classification of AKI in the ICU (40-42). This is consistent with our findings that the association of R class with mortality was not statistically significant, and that maximum renal dysfunction during the ICU stay was reached within a two-day period in most patients. Furthermore, classifying any patients receiving RRT as stage 3 is questionable and may introduce bias due to the lack of uniform recommendations regarding the timing and modalities of RRT.

Second, we encountered the same problem as others (17, 20): the 6- and 12-hrs urine outputs were not recorded in our database. Therefore, patients were classified according to the GFR criteria only. Patients classified according the GFR criteria seem to be more severely ill and have slightly higher mortality rates than their counterparts classified according to the urine output criteria (16, 43, 44). Having considered both criteria may have resulted in a lowest estimation of the risk of death (and a higher incidence of AKI).

Third, although recommended by the ADQI group (10), the MDRD equation for estimation of baseline creatinine values may be questionable. Further investigations comparing the diagnostic accuracy of observed or estimated creatinine to that of novel serum or urine biomarkers, such as cystatin C or neutrophil-gelatinase associated lipocalin (45-50), are warranted.

Fourth, the extent to which RRT interferes with AKI patients' prognosis remains unclear and practices regarding this technique vary widely from one institution to another. Consequently, considering RRT as a confounder could have lead to hazardous conclusions. This issue deserves further specific evaluation.

Fifth, our database does not contain any information after hospital discharge. Thus, we were unable to assess long-term renal function and prognosis.

Sixth, although multiple-center, our database is not multinational. So, our population may not be representative of ICU patients in other countries. Nevertheless, baseline characteristics, incidence of ARF and proportion of patients receiving RRT were similar as those reported in previous studies (16, 20).

Finally, we did not have any information as to the exact etiology of AKI, although sepsis was probably the commonest one. Of note, a recent study revealed that RIFLE classification could be used to evaluate the overall prognosis of septic patients, suggesting a close link between AKI and sepsis (51). However, AKI often results from a combination of several risk factors, whose respective contributions are difficult to determine. Whether any of these risk factors plays a preponderant role or prognosis differs according to the cause leading to AKI remains unknown.

## **CONCLUSIONS**

While the prognosis of AKI has long remained unclear due to the lack of a uniform definition, the recently published RIFLE criteria have facilitated epidemiological research in the field. Three multiple-center studies using conventional statistical models found an association between RIFLE classes and mortality (16, 18, 20). Original multi-state, competing risks models reflecting “real life” more accurately are now available but are rarely used in the ICU setting. By applying such a model, we found that AKI was an overall predictor of poor outcome, with some interesting differences between RIFLE classes. While there was only a trend towards an increased risk of death in those patients with a moderate renal dysfunction (R class), a sustained and more severe deterioration of renal function had a major negative impact, the maximum risk of death being reached as soon as patients were on I class. Further investigations focusing on the impact of RRT are warranted to confirm these results.

## REFERENCES

1. Kellum JA, Levin N, Bouman C, et al: Developing a consensus classification system for acute renal failure. *Curr Opin Crit Care* 2002; 8:509-514
2. Chertow GM, Christiansen CL, Cleary PD, et al: Prognostic stratification in critically ill patients with acute renal failure requiring dialysis. *Arch Intern Med* 1995; 155:1505-1511
3. Cosentino F, Chaff C, Piedmonte M: Risk factors influencing survival in ICU acute renal failure. *Nephrol Dial Transplant* 1994; 9 Suppl 4:179-182
4. de Mendonca A, Vincent JL, Suter PM, et al: Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. *Intensive Care Med* 2000; 26:915-921
5. Liano F, Junco E, Pascual J, et al: The spectrum of acute renal failure in the intensive care unit compared with that seen in other settings. The Madrid Acute Renal Failure Study Group. *Kidney Int Suppl* 1998; 66:S16-24
6. Mehta RL, Pascual MT, Soroko S, et al: Spectrum of acute renal failure in the intensive care unit: the PICARD experience. *Kidney Int* 2004; 66:1613-1621
7. Neveu H, Kleinknecht D, Brivet F, et al: Prognostic factors in acute renal failure due to sepsis. Results of a prospective multicentre study. The French Study Group on Acute Renal Failure. *Nephrol Dial Transplant* 1996; 11:293-299
8. Schaefer JH, Jochimsen F, Keller F, et al: Outcome prediction of acute renal failure in medical intensive care. *Intensive Care Med* 1991; 17:19-24
9. Uchino S, Kellum JA, Bellomo R, et al: Acute renal failure in critically ill patients: a multinational, multicenter study. *Jama* 2005; 294:813-818
10. Bellomo R, Ronco C, Kellum JA, et al: 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:R204-212
11. Ahlstrom A, Kuitunen A, Peltonen S, et al: Comparison of 2 acute renal failure severity scores to general scoring systems in the critically ill. *Am J Kidney Dis* 2006; 48:262-268
12. Kuitunen A, Vento A, Suojaranta-Ylinen R, et al: Acute renal failure after cardiac surgery: evaluation of the RIFLE classification. *Ann Thorac Surg* 2006; 81:542-546
13. Lopes JA, Jorge S, Neves FC, et al: An assessment of the RIFLE criteria for acute renal failure in severely burned patients. *Nephrol Dial Transplant* 2007; 22:285
14. Lopes JA, Jorge S, Silva S, et al: An assessment of the RIFLE criteria for acute renal failure following myeloablative autologous and allogeneic haematopoietic cell transplantation. *Bone Marrow Transplant* 2006; 38:395
15. Abosaif NY, Tolba YA, Heap M, et al: The outcome of acute renal failure in the intensive care unit according to RIFLE: model application, sensitivity, and predictability. *Am J Kidney Dis* 2005; 46:1038-1048
16. Hoste EA, Clermont G, Kersten A, et al: RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. *Crit Care* 2006; 10:R73
17. Uchino S, Bellomo R, Goldsmith D, et al: An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. *Crit Care Med* 2006; 34:1913-1917
18. Bagshaw SM, George C, Dinu I, et al: A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. *Nephrol Dial Transplant* 2008; 23:1203-1210

19. Maccariello E, Soares M, Valente C, et al: RIFLE classification in patients with acute kidney injury in need of renal replacement therapy. *Intensive Care Med* 2007; 33:597-605
20. Ostermann M, Chang RW: Acute kidney injury in the intensive care unit according to RIFLE. *Crit Care Med* 2007; 35:1837-1843; quiz 1852
21. Wolkewitz M, Beyersmann J, Gastmeier P, et al: Modeling the effect of time-dependent exposure on intensive care unit mortality. *Intensive Care Med* 2009; 35:826-832
22. Wolkewitz M, Vonberg RP, Grundmann H, et al: Risk factors for the development of nosocomial pneumonia and mortality on intensive care units: application of competing risks models. *Crit Care* 2008; 12:R44
23. Putter H, Fiocco M, Geskus RB: Tutorial in biostatistics: competing risks and multi-state models. *Stat Med* 2007; 26:2389-2430
24. Beyersmann J, Gastmeier P, Grundmann H, et al: Use of multistate models to assess prolongation of intensive care unit stay due to nosocomial infection. *Infect Control Hosp Epidemiol* 2006; 27:493-499
25. Resche-Rigon M, Azoulay E, Chevret S: Evaluating mortality in intensive care units: contribution of competing risks analyses. *Crit Care* 2006; 10:R5
26. Schumacher M, Wangler M, Wolkewitz M, et al: Attributable mortality due to nosocomial infections. A simple and useful application of multistate models. *Methods Inf Med* 2007; 46:595-600
27. Clec'h C, Alberti C, Vincent F, et al: Tracheostomy does not improve the outcome of patients requiring prolonged mechanical ventilation: a propensity analysis. *Crit Care Med* 2007; 35:132-138
28. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: a severity of disease classification system. *Crit Care Med* 1985; 13:818-829
29. Fine J, Gray JR: A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; 94:496-509
30. Andersen P, Abildstrom S, Rosthøj S: Competing risks as a multi-state model. *Stat Methods Med Res* 2002; 11:203-215
31. Pepe MS, Mori M: Kaplan-Meier, marginal or conditional probability curves in summarizing competing risks failure time data? *Stat Med* 1993; 12:737-751
32. Beyersmann J, Schumacher M: Time-dependent covariates in the proportional subdistribution hazards model for competing risks. *Biostatistics* 2008; 9:765-776
33. Azoulay E, Alberti C, Bornstain C, et al: Improved survival in patients in cancer patients requiring mechanical ventilatory support: impact of noninvasive ventilatory support. *Crit Care Med* 2001; 29:519-525
34. de Irala-Estevez J, Martinez-Concha DD-M, C., Masa-Calles J, et al: Comparison of different methodological approaches to identify risk factors of nosocomial infection in intensive care units. *Intensive Care Med* 2001; 27:1254-1262
35. Alberti C, Metivier F, Landais P, et al: Improving estimates of event incidence over time in populations exposed to other events: application to three large databases. *J Clin Epidemiol* 2003; 56:536-545
36. Beyersmann J, Gastmeier P, Wolkewitz M, et al: An easy mathematical proof showed that time-dependent bias inevitably leads to biased effect estimation. *J Clin Epidemiol* 2008; 61:1216-1221
37. van Walraven C, Davis D, Forster AJ, et al: Time-dependent bias was common in survival analyses published in leading clinical journals. *J Clin Epidemiol* 2004; 57:672-682
38. Chertow GM, Burdick E, Honour M, et al: Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005; 16:3365-3370
39. Mehta RL, Kellum JA, Shah SV, et al: Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; 11:R31

40. 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; 23:1569-1574
41. Joannidis M, Metnitz B, Bauer P, et al: Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. *Intensive Care Med* 2009; 35:1692-1702
42. Lopes JA, Fernandes P, Jorge S, et al: Acute kidney injury in intensive care unit patients: a comparison between the RIFLE and the Acute Kidney Injury Network classifications. *Crit Care* 2008; 12:R110
43. Hoste EA, Kellum JA: Acute kidney injury: epidemiology and diagnostic criteria. *Curr Opin Crit Care* 2006; 12:531-537
44. Cruz D, Ricci Z, Ronco C: Clinical review: RIFLE and AKIN--time for reappraisal. *Crit Care* 2009; 13:211
45. Ahlstrom A, Tallgren M, Peltonen S, et al: Evolution and predictive power of serum cystatin C in acute renal failure. *Clin Nephrol* 2004; 62:344-350
46. Delanaye P, Lambermont B, Chapelle JP, et al: Plasmatic cystatin C for the estimation of glomerular filtration rate in intensive care units. *Intensive Care Med* 2004; 30:980-983
47. Herget-Rosenthal S, Marggraf G, Husing J, et al: Early detection of acute renal failure by serum cystatin C. *Kidney Int* 2004; 66:1115-1122
48. Mishra J, Dent C, Tarabishi R, et al: Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet* 2005; 365:1231-1238
49. Nickolas TL, O'Rourke MJ, Yang J, et al: Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. *Ann Intern Med* 2008; 148:810-819
50. Zappitelli M, Washburn KK, Arikian AA, et al: Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children: a prospective cohort study. *Crit Care* 2007; 11:R84
51. Chen YC, Jenq CC, Tian YC, et al: Rife classification for predicting in-hospital mortality in critically ill sepsis patients. *Shock* 2009; 31:139-145

## APPENDIX

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**Table 1. RIFLE classification.**

RIFLE class	GFR criteria	UO criteria
Risk	Increase in serum creatinine $\geq 1.5$ X baseline or decrease in GFR $\geq 25$ %	$< 0.5$ ml/kg/h for $\geq 6$ hrs
Injury	Increase in serum creatinine $\geq 2$ X baseline or decrease in GFR $\geq 50$ %	$< 0.5$ ml/kg/h for $\geq 12$ hrs
Failure	Increase in serum creatinine $\geq 3$ X baseline or decrease in GFR $\geq 75$ % or serum creatinine $\geq 350$ $\mu\text{mol/L}$ with an acute rise of at least $44$ $\mu\text{mol/L}$	$< 0.3$ ml/kg/h for $\geq 24$ hrs or anuria $\geq 12$ hrs
Loss	Complete loss of kidney function $> 4$ weeks	
End-stage kidney disease	Need for RRT $> 3$ months	

GFR, glomerular filtration rate; UO, urine output; RRT, renal replacement therapy.

**Table 2. Baseline characteristics of patients with and those without AKI.**

Variable	Patients with AKI	Patients without AKI	<i>P</i> value
	(n = 2846)	(n = 5793)	
Age, mean (SD)	66.4 (15.9)	55.6 (18.5)	< 0.0001
Males, no. (%)	1672 (58.8)	3609 (62.3)	0.002
SAPS II score, mean (SD)	50.2 (20.0)	33.6 (16.9)	< 0.0001
APACHE II score, mean (SD)	19.9 (7.1)	12.9 (6.4)	< 0.0001
Transfer from ward, no. (%)	1363 (47.9)	2494 (43.1)	< 0.0001
McCabe, no. (%)			
1	1666 (58.5)	4074 (70.3)	
2	959 (33.7)	1417 (24.5)	
3	221 (7.8)	302 (5.2)	< 0.0001
Admission category, no. (%)			
Medical	2043 (71.8)	4149 (71.6)	
Scheduled surgery	311 (10.9)	865 (14.9)	
Unscheduled surgery	492 (17.3)	779 (13.5)	< 0.0001
Chronic coexisting conditions, no. (%)			
Cardiac disease	509 (17.9)	497(8.6)	< 0.0001
Respiratory disease	366 (12.9)	881 (15.2)	0.004
Liver disease	178 (6.3)	288 (5.0)	0.01
Immunodeficiency	440 (15.5)	688 (11.9)	< 0.0001
Uncomplicated diabetes mellitus	320 (11.2)	431 (7.4)	< 0.0001
Complicated diabetes mellitus	148 (5.2)	124 (2.1)	< 0.0001

AKI, acute kidney injury; SAPS, Simplified Acute Physiology Score; APACHE, Acute Physiology and Chronic Health Evaluation.

**Table 3. Baseline characteristics of AKI patients according to the maximum RIFLE class reached during the intensive care unit stay.**

Variable	Class R patients	Class I patients	Class F patients	P value
	(n = 1025)	(n = 830)	(n = 991)	
Age, mean (SD)	67.6 (15.8)	66.7 (15.7)	64.9 (16.0)	< 0.001
Males, no. (%)	588 (57.4)	502 (60.5)	582 (58.7)	0.4
SAPS II score, mean (SD)	45.2 (17.4)	51.9 (21.2)	53.8 (20.3)	< 0.0001
APACHE II score, mean (SD)	18 (6.6)	20.6 (7.1)	21.4 (7.1)	< 0.0001
Transfer from ward, no. (%)	477 (46.5)	387 (46.6)	499 (50.4)	0.16
<i>McCabe, no. (%)</i>				
1	608 (59.3)	476 (57.3)	582 (58.7)	
2	342 (33.4)	290 (35.0)	327 (33)	
3	75 (7.3)	64 (7.7)	82 (8.3)	0.8
<i>Admission category, no. (%)</i>				
Medical	754 (73.6)	592 (71.3)	697 (70.3)	
Scheduled surgery	130 (12.7)	85 (10.2)	96 (9.7)	
Unscheduled surgery	141 (13.8)	153 (18.4)	198 (20.0)	<0.002
<i>Chronic coexisting conditions, no. (%)</i>				
Cardiac disease	185 (18.1)	163 (19.6)	161 (16.3)	0.2
Respiratory disease	165 (16.1)	101 (12.2)	100 (10.1)	< 0.001
Liver disease	61 (6.0)	59 (7.1)	58 (5.9)	0.5
Immunodeficiency	143 (14.0)	137 (16.5)	160 (16.2)	0.2
Uncomplicated diabetes	125 (12.2)	90 (10.8)	105 (10.6)	0.5
mellitus				
Complicated diabetes	45 (4.4)	40 (4.8)	63 (6.4)	0.1
mellitus				

AKI, acute kidney injury; SAPS, Simplified Acute Physiology Score; APACHE, Acute Physiology and Chronic Health Evaluation.

**Table 4. Impact of acute kidney injury (AKI) on intensive care unit (ICU) and hospital mortality: results of the unadjusted and adjusted Fine and Gray models.**

Variable	SHR, 95% CI	<i>P</i>	SHR, 95% CI	<i>P</i>
	univariate analysis		multivariate analysis	
	<b><i>ICU mortality</i></b>			
No AKI	1	-	1	-
R class	2.90 [2.35-3.58]	< 0.0001	1.01[0.81-1.26]	0.9
I class	9.98 [8.39-11.89]	< 0.0001	2.80 [2.33-3.36]	< 0.0001
F class	8.28 [7.01-9.79]	< 0.0001	2.46 [2.04-2.95]	< 0.0001
SAPS II score, per point	-	-	1.056 [1.053-1.059]	< 0.0001
Mc Cabe class 3	-	-	1.82 [1.53-2.17]	< 0.0001
Respiratory failure	-	-	3.22 [1.27-8.13]	0.01
	<b><i>Hospital mortality</i></b>			
No AKI	1	-	1	-
R class	2.30 [1.93-2.74]	< 0.0001	1.16 [0.97-1.39]	0.09
I class	6.21 [5.35-7.21]	< 0.0001	2.42 [2.06-2.84]	< 0.0001
F class	5.62 [4.88-6.47]	< 0.0001	2.18 [1.87-2.56]	< 0.0001
SAPS II score, per point	-	-	1.048 [1.046-1.051]	< 0.0001
Mc Cabe class 3	-	-	1.85 [1.58-2.15]	< 0.0001
Respiratory failure	-	-	3.56 [1.50-8.44]	< 0.01

SHR, sub-hazard ratio; CI, confidence interval; SAPS, Simplified Acute Physiology Score.

**Table 5. Lengths of intensive care unit (ICU) and hospital stays in patients with and without acute kidney injury (AKI).**

Variable	No AKI	Class R patients	Class I patients	Class F patients	<i>P</i> value
		(n = 1025)	(n = 830)	(n = 991)	
ICU stay, days	4 [3-7]	6 [3-11]	7 [4-12]	8 [4-17]	< 0.001
Hospital stay, days	16 [9-30]	22 [12-40]	21 [10-37]	25 [12-44]	< 0.001

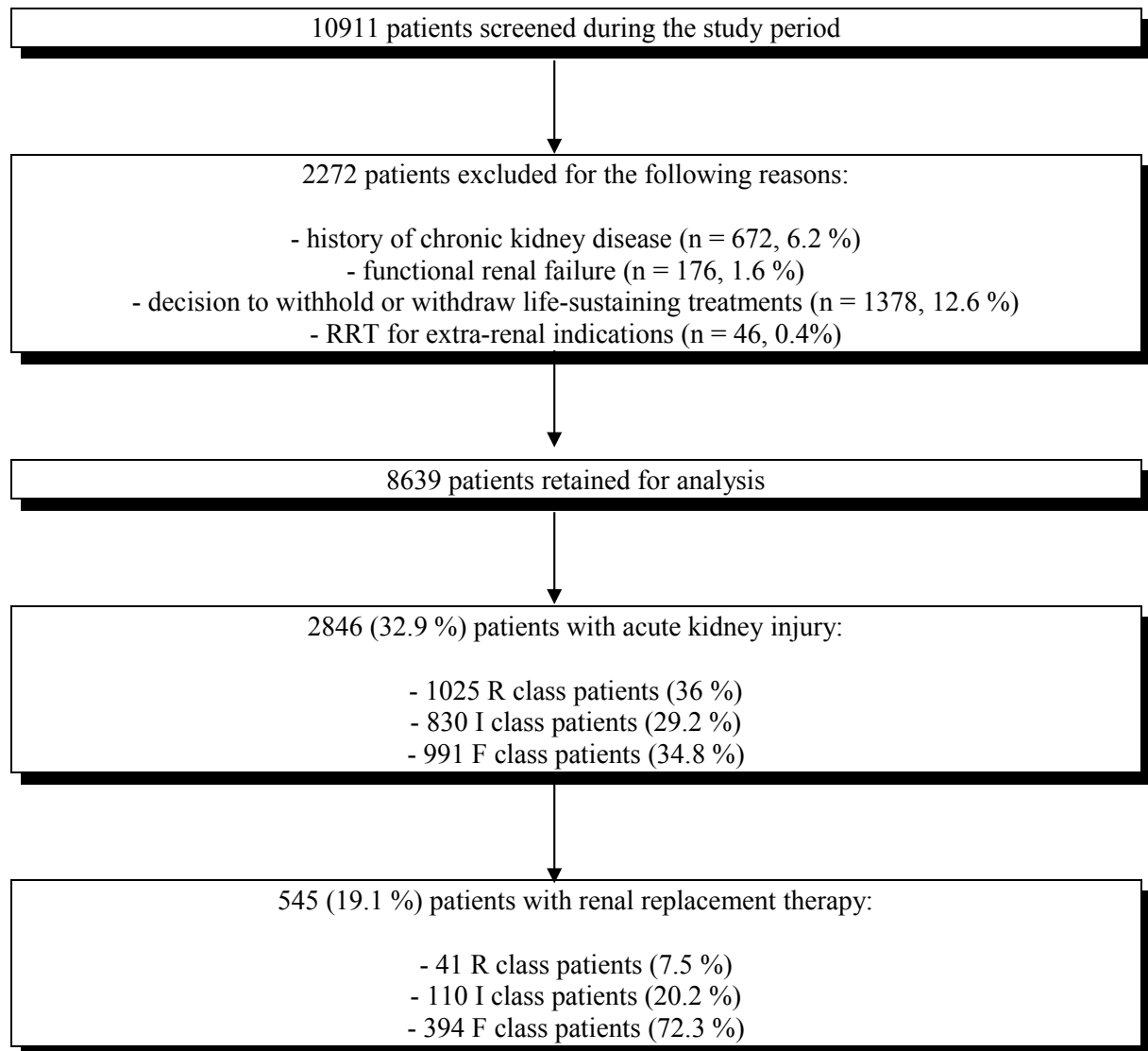
Results are expressed as median [interquartile range].

**Table 6. Differences in SAPS II scores and mortality rates between patients with and without renal replacement therapy (RRT) according to the maximum RIFLE class reached during the intensive care unit (ICU) stay.**

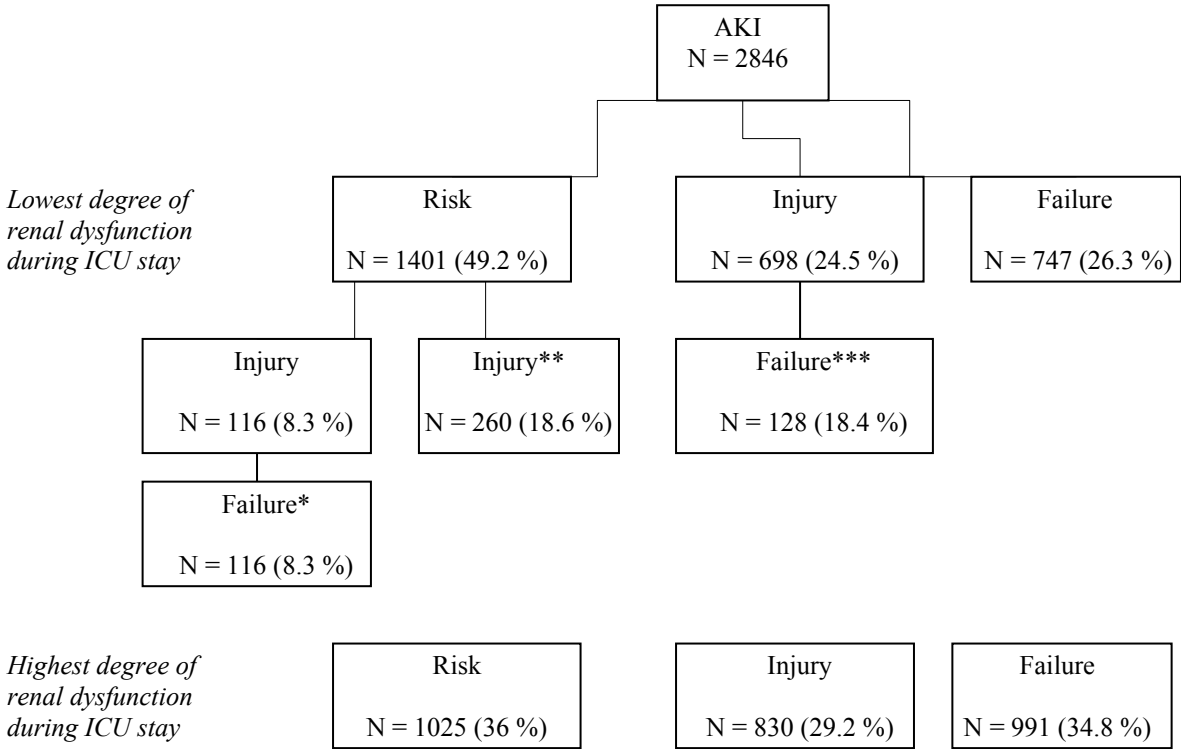
	RRT	No RRT	<i>P</i> value
<i>R class</i>	N = 41	N = 984	
SAPS II score, mean (SD)	57.6 (20.4)	45.7 (17.1)	< 0.001
ICU mortality, %	46.3	10.3	< 0.0001
Hospital mortality, %	61	14.8	< 0.0001
<i>I class</i>	N = 110	N = 720	
SAPS II score, mean (SD)	61.9 (21.2)	50.4 (20.8)	< 0.001
ICU mortality, %	53.6	23.6	< 0.0001
Hospital mortality, %	60.9	29.7	< 0.0001
<i>F class</i>	N = 394	N = 597	
SAPS II score, mean (SD)	55.3 (18.2)	52.8 (21.6)	< 0.001
ICU mortality, %	32.7	22.1	< 0.001
Hospital mortality, %	39.1	29.8	0.003

SAPS, Simplified Acute Physiology Score.

**Figure 1. Study flow chart**



**Figure 2. Dynamics of acute kidney injury (AKI) during the intensive care unit (ICU) stay.**



The flowchart illustrates the lowest and highest degrees of renal dysfunction reached during the ICU stay, and the proportions of patients displaying a progressive alteration of their kidney function.

\* forty patients moved from R to F class of RIFLE despite having received renal replacement therapy (38 while on R class, and two while on I class).

\*\* thirty-eight patients moved from R to I class of RIFLE despite having received renal replacement therapy while still on R class.

\*\*\* twenty-five patients moved from I to F class of RIFLE despite having received renal replacement therapy while still on I class.



# **Deuxième partie**

*Place de l'épuration extra-rénale*

## II.1 Considérations épidémiologiques

La prise en charge de l'AKI en réanimation repose exclusivement sur les mesures de prévention secondaire et sur la suppléance par EER. Bien que cette dernière puisse être considérée comme la pierre angulaire du traitement, faute d'alternative curative, son impact pronostique reste incertain. Alors qu'il serait logique d'en escompter un bénéfice important de par la correction des perturbations métaboliques, le contrôle de la surcharge hydro-sodée et la possibilité de fournir un apport nutritionnel adapté à des patients en état d'hypercatabolisme intense, les données de la littérature révèlent des taux de mortalité plus élevés chez les patients épurés que chez les patients non épurés : <sup>11, 12, 16, 32, 33</sup>

Etude	Année	N	Schéma et lieu	Mortalité (%)	
				Sans EER	Avec EER
Brivet et al (32)	1996	360	Multicentrique, France	43%	64%
Liano et al (11)	1998	748	Multicentrique, Espagne	53%	79%
Metnitz et al (16)	2002	839	Multicentrique, Autriche	39%	63%
Mehta et al (33)	2002	605	Multicentrique, USA	39%	61%
Mehta et al (12)	2004	618	Multicentrique, USA	24%	45%

Pour surprenante qu'elle soit, cette différence de mortalité entre patients épurés et non épurés ne doit toutefois pas amener à conclure hâtivement que l'EER est inefficace, voire nocive, mais pousser au contraire à rechercher des raisons logiques susceptibles d'expliquer un paradoxe qui ne serait qu'apparent. Ainsi l'analyse des études disponibles met en évidence

plusieurs points cruciaux qui rendent effectivement difficile et hasardeuse l'estimation de l'efficacité de l'EER.

Tout d'abord, bien que les comparaisons directes des caractéristiques de base entre patients épurés et non épurés soient rares, les premiers semblent avoir davantage de comorbidités et de défaillances d'organes que les seconds. Soulignons que cette particularité suggérée par les travaux de Metnitz et de Mehta se retrouve également dans l'étude présentée plus loin (chapitre II.3).<sup>12, 16</sup> Le recours à l'EER peut donc s'interpréter comme un marqueur de sévérité globale, et non comme un traitement, expliquant la surmortalité observée.

Ensuite, le délai d'instauration de l'EER n'est pas précisé, ou imprécis tout au moins, dans la plupart des publications. Or, ce délai pourrait avoir une influence majeure sur les résultats en ce sens qu'un début trop tardif, à un stade avancé de dysfonction rénale avec défaillance multiviscérale, n'est évidemment pas de nature à favoriser la démonstration d'un effet bénéfique de l'EER. Toutefois, cette hypothèse n'est pas démontrée formellement et les résultats divergent en fonction de la définition du caractère précoce de l'EER.<sup>1</sup>

Enfin, du fait de l'absence d'indications claires et consensuelles malgré la publication récente de recommandations internationales pour la prévention et la prise en charge de l'AKI en réanimation,<sup>3</sup> la décision de mettre ou non un patient sous EER peut être largement influencée par des caractéristiques propres aux patients ou par des événements survenant en cours de séjour qui sont également liés au devenir des patients. L'effet propre de l'EER devient alors impossible à déterminer.

Seul un essai contrôlé randomisé définissant précisément les indications, le délai d'instauration et les modalités de l'EER permettrait d'établir l'efficacité réelle de la technique. Un tel essai paraissant cependant peu envisageable en réanimation, les connaissances dans le domaine continueront sans doute à reposer sur des études observationnelles dont la validité sera nécessairement conditionnée par le choix d'une

méthodologie statistique adaptée, propre à en minimiser les nombreux biais. Ce thème fait l'objet du chapitre suivant.

## II.2 Considérations méthodologiques

Plaçons-nous dans l'optique de l'évaluation de l'impact d'un traitement sur la mortalité en réanimation.

Dans un essai contrôlé, randomisé, contre placebo, l'allocation aléatoire du traitement conduit en théorie à une répartition équilibrée des variables de confusion entre les groupes, tant pour les variables mesurées que pour les variables non mesurées. Ainsi, la différence de mortalité observée ne dépend-elle que de l'effet du traitement. La comparaison entre les groupes de traitement ne pose alors pas de problème particulier et peut se faire au moyen de tests statistiques simples.

Dans une étude observationnelle, en revanche, la répartition par définition non équilibrée des nombreuses variables de confusion entraîne un fort risque d'estimation biaisée de l'effet du traitement. Le choix de la méthodologie est par conséquent crucial dans ce type d'études pour minimiser le risque de conclusions erronées.

Les trois stratégies les plus couramment utilisées pour contrôler le biais de confusion sont l'appariement, la stratification, et l'ajustement via des modèles de régression logistique multivariée. L'appariement consiste à créer des sous-groupes de patients, composés de  $m$  sujets traités et de  $n$  sujets non traités, en imposant que les valeurs des variables de confusion soient identiques ou très proches chez les sujets traités et non traités. L'effet du traitement est alors estimé à l'intérieur de chaque sous-groupe entre patients homogènes pour la ou les variable(s) de confusion. La difficulté à appairer liée à un nombre trop important de variables de confusion et le risque de surappariement sont les deux inconvénients principaux de cette méthode. Le principe de la stratification est voisin. Les patients sont séparés en classes (strates) selon différentes valeurs d'une variable de confusion donnée. Les comparaisons intra-classes permettent de faire « disparaître » l'effet de cette variable et de fournir une estimation plus fiable de l'effet du traitement. Là encore, un nombre trop important de

variables de confusion rend la méthode inopérante. En effet, le total de strates à créer,  $N^k$  (où  $N$  est le nombre de strates par variable de confusion et  $k$  le nombre de variables de confusion à prendre en compte), augmente de façon exponentielle, créant non seulement un problème évident de faisabilité mais exposant également au risque de strates extrêmes constituées uniquement de patients traités ou au contraire non traités avec impossibilité d'estimer l'effet du traitement. La gestion des variables de confusion est plus aisée avec les modèles de régression logistique multivariée. Cependant, le nombre de variables sur lesquelles il est possible d'ajuster est conditionné par la fréquence de l'événement d'intérêt (une variable de confusion pour 10 événements d'intérêt). De plus, si les groupes de traitement sont très hétérogènes pour une variable de confusion donnée, le chevauchement insuffisant, voire inexistant, des valeurs de cette variable entre les groupes de traitement engendre une estimation biaisée ou impossible de son effet et peut compromettre la fiabilité du modèle.

Outre leurs limites intrinsèques, appariement, stratification et ajustement ne sont pas adaptés à un type de biais particulier : le biais de sélection de traitement. L'exposition à ce biais survient lorsque le traitement ou la procédure à l'étude ne font pas l'objet d'indications claires et consensuelles, comme cela est le cas pour l'EER. Dans cette situation, la décision d'instituer ou non le traitement est largement influencée par les caractéristiques propres aux patients (sévérité, comorbidités) ainsi que par des événements survenant en cours de séjour en réanimation (arrêt cardio-circulatoire, SDRA réfractaire), eux-mêmes liés au pronostic. L'estimation de l'effet propre du traitement est alors extrêmement difficile à établir et des méthodes statistiques spécifiques sont donc indiquées.

La technique du score de propension (SP) décrite au début des années 80 s'affirme comme une solution élégante pour contrôler le biais de sélection de traitement.<sup>34-36</sup> Son application se déroule en trois étapes : la construction du score, la vérification de sa validité et son utilisation proprement dite pour appairer, stratifier ou ajuster.

La construction du SP se fait par l'intermédiaire d'un modèle de régression logistique multivariée dans lequel la variable à expliquer est le traitement. Le SP pouvant s'interpréter comme la probabilité de recevoir le traitement étudié, les variables explicatives sont naturellement liées au traitement en question. Toutefois se limiter à ces seules variables entraîne deux écueils. D'une part le modèle risque d'être trop discriminant et de compromettre les possibilités d'appariement, de stratification et d'ajustement, réduisant de la sorte fortement l'intérêt du SP ; d'autre part, l'estimation de l'effet du traitement est susceptible de rester biaisée et sa variance, en tout cas, s'en trouve augmentée. Pour pallier ces écueils, il est recommandé d'introduire également des variables liées au pronostic.<sup>37, 38</sup> Le choix final des variables explicatives à retenir parmi les variables candidates potentielles ne repose sur aucun critère absolu. On se base en général sur les études publiées antérieurement pour tenter de déterminer les « indications » les plus courantes du traitement étudié. A défaut, les variables peuvent être sélectionnées par un groupe d'experts selon la méthode Delphi. Cette méthode développée à la fin des années 40 est largement utilisée dans les domaines politique, économique et social mais relativement peu en médecine.<sup>39</sup> Brièvement, un sondage d'opinion touchant un domaine encore peu ou pas exploré est réalisé dans un premier temps, suivi dans un deuxième temps d'un nouveau questionnaire établi à partir de l'analyse des réponses aux questions précédentes. Le but est de « créer » de l'information dans le domaine et de parvenir à un consensus en deux à cinq étapes avec 10 à 30 experts qui peuvent à chaque nouveau questionnaire reconsidérer leur opinion à la lumière des avis émis par les autres.<sup>40, 41</sup> D'autres méthodes de choix des variables explicatives (modèle non parcimonieux incluant toutes les différences entre patients traités et non traités mises en évidence en analyse univariée, sélection pas à pas des variables maximisant l'adéquation du modèle) sont aussi utilisées mais paraissent moins appropriées et ne sont pas recommandées.<sup>42-44</sup>

Des patients traités et non traités se retrouvant fatalement avec le même SP en l'absence d'indications consensuelles au traitement, tout se passe comme si le traitement était alloué « au hasard », effaçant en grande partie les biais de l'étude inhérents à son caractère observationnel et la ramenant au rang d'essai « quasi-randomisé ».

Après la construction du SP, la vérification de sa validité est l'étape indispensable préalable à son utilisation. Plus précisément, il convient de s'assurer que les variables explicatives (prédictives) du traitement retenues dans le modèle sont distribuées de façon équilibrée entre patients traités et non traités ayant un SP identique ou proche.

Une fois sa validité établie, le SP peut s'exploiter de plusieurs manières. La stratification est la première d'entre elles, cinq strates permettant habituellement d'éliminer 90% du biais.<sup>45</sup> L'appariement est une autre option courante peut-être plus performante puisque réduisant semble-t-il le risque de biais et la variance de l'estimation de l'effet du traitement (ref).<sup>46</sup> Enfin, le SP peut être utilisé comme covariable d'ajustement (explicative) dans le modèle final où la variable à expliquer est l'effet du traitement. Dans ce cas, il faut prendre garde de ne pas introduire comme autres covariables des variables ayant servi à la construction du SP pour éviter les soucis de colinéarité.

Ainsi, lorsque un essai thérapeutique contrôlé randomisé est impossible d'un point de vue pratique ou éthique, le SP est un outil très précieux. Un exemple d'application est donné dans le chapitre suivant.



## II.3 Application

Cet article se propose d'évaluer l'impact de l'EER chez des patients de réanimation avec AKI, par la technique du SP. Il a été soumis pour publication à « *Journal of the American Society of Nephrology* ».

Il s'agit de la première évaluation à grande échelle de l'efficacité de l'EER. Les résultats suggèrent qu'elle n'améliore pas le pronostic des patients, du moins telle qu'elle est pratiquée actuellement, et posent le problème de son délai d'instauration.

**Impact of renal replacement therapy on the outcome of intensive care unit patients with acute kidney injury: a propensity analysis.**

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## **ABSTRACT**

Although renal replacement therapy (RRT) being a common procedure in critically ill patients with acute kidney injury (AKI), its efficacy remains uncertain. Patients who receive RRT usually have higher mortality rates than those who do not. However, there are many differences in severity patterns between patients with and those without RRT and available results are further confounded by treatment selection bias since no consensus on indications for RRT has been reached so far. The aim of this multicentric observational study was to account for these biases to accurately assess RRT efficacy, with special attention to RRT timing. A propensity score for RRT was built to match patients who received RRT to controls who did not despite having the same probability of receiving the procedure. AKI was defined according to RIFLE criteria. The association between RRT and intensive care unit (ICU) mortality was examined through a multivariate conditional logistic regression model to control for residual confounding. Among the 2846 study patients, 545 (19%) received RRT. Crude mortality rates were higher in patients with than in those without RRT (38% vs 17.5%,  $p < 0.001$ ). After matching and adjustment, RRT was not associated with improved ICU survival, whatever the RIFLE class. In F class patients, late RRT (initiated more than 24 hrs after reaching maximum RIFLE class) was significantly associated with ICU mortality (odds ratio: 5.90;  $p < 0.001$ ). Our results suggest that current RRT practices may be inappropriate and stress the need for urgent standardization of indications and timing of RRT.

## INTRODUCTION

Acute kidney injury (AKI) significantly contributes to the morbidity and the mortality of critically ill patients through metabolic derangements, fluid overload and harmful effects of these disturbances on other failing organs. Renal replacement therapy (RRT), although not achieving the same level of homeostasis as a normally functioning kidney, helps limit the consequences of the decline in kidney function and allows adequate administration of necessary fluids and nutritional support. Accordingly, RRT is anticipated to be an effective treatment in critically ill patients with AKI. However, patients who receive RRT have usually higher mortality rates than patients who do not,<sup>1-5</sup> and evidence that RRT improves patients' prognosis is lacking (aside from life-threatening complications, such as severe hyperkalemia, pulmonary edema, and intractable acidosis).

A randomized controlled trial of RRT vs no RRT in the intensive care unit (ICU) being hard to imagine, data on the impact of RRT will probably continue to stem from observational studies. This emphasizes the utmost importance of rigorous statistical analyses to reduce as much as possible the risk of bias and provide reliable results. Particularly, observational studies in the field are subjected to treatment selection bias (also called « confounding by indication »).<sup>6</sup> This kind of bias occurs when no consensual indications exist for a given treatment or procedure, which is undoubtedly the case for RRT despite the recent publication of recommendations for the prevention and management of AKI in the ICU.<sup>7</sup> The decision to start RRT being based on poorly defined empirical criteria, the association between RRT and outcomes may be confounded by patients' characteristics and influenced by in-ICU events also related to outcomes, leading to inconclusive results. The propensity score described by Rosenbaum and Rubin is a powerful method to control for treatment selection bias.<sup>8, 9</sup> It

makes possible to assess the association of a procedure with specific outcomes in patients with an equal probability of receiving the procedure.

The aim of this study was to use the propensity technique to yield an accurate estimation of the association of RRT with ICU mortality. Specifically, we addressed the impact of timing of RRT.

## **RESULTS**

### *Study patients*

The study included 2846 patients with AKI, of whom 545 (19.1 %) received RRT (figure 1, electronic supplementary material -ESM-).

Patients who received RRT were younger, had higher severity scores, were more likely to be transferred from ward, and presented more comorbidities than patients who did not receive RRT (table 1). Differences according to the maximum RIFLE class reached during the ICU stay are shown in tables 1, 2 and 3 of the ESM.

### *Dynamics of AKI and timing of renal replacement therapy*

AKI was a rapidly evolving process. Times from ICU admission to maximum RIFLE class were 1 [1-2], 2 [1-3], and 2 [1-3] in R, I, and F classes patients, respectively.

Time to initiation of RRT after reaching maximum RIFLE class was 0 [0-1]. RRT was initiated early (ie, less than 24 hours after reaching maximum RIFLE class) in 479 (87.9%) patients. Differences in serum creatinine between patients who actually received RRT and those who did not on reaching maximum RIFLE class are presented in table 2.

### *Impact of renal replacement therapy*

RRT resulted in longer lengths of ICU stay after reaching maximum RIFLE class (tables 4 and 5, ESM) but did not improve survival. Crude ICU mortality rates of patients with and without RRT were 38% and 17.5%, respectively ( $p < 0.001$ ). Among patients who received RRT, 92 of the 338 survivors (27.2 %) still needed renal support on ICU discharge.

Of the 545 patients who received RRT, 522 (95.8%) could be matched to 955 controls having a similar probability of receiving RRT (ie, a difference in propensity scores  $\leq 5\%$ ) but who did not receive RRT. There were no differences in serum creatinine on RRT initiation between matched patients with and those without RRT (table 3), thus confirming the ability of the propensity score to control for treatment selection bias. In univariate analysis, patients who received RRT had higher mortality rates than their respective controls (37% vs 15%,  $p < 0.001$ ). After adjustment for residual confounding, namely differences in organ failures reflected by the non-renal SOFA score (SOFA score-renal component) computed on initiation of RRT or on the corresponding time in controls (table 4), RRT was not associated with an improved ICU survival, whatever its timing. This was true for any of the R, I, and F classes. In F class patients, late RRT (ie, initiated more than 24 hrs after reaching maximum RIFLE class) was even associated with an increased ICU mortality (table 4).

## **DISCUSSION**

While the impact of RRT modalities has been widely investigated through randomized controlled trials,<sup>10-15</sup> the overall efficacy of RRT remains uncertain. Actually, there is no real head to head comparison of AKI patients with and without RRT in the current literature. Mortality rates are usually higher in patients with than in those without RRT.<sup>1-5</sup> However, no definitive conclusions can be drawn from these data due to the absence of clear

indications for RRT and the many differences in severity patterns between patients who receive RRT and those who do not. In other words, treatment selection bias and patients underlying severity are major confounders making the assessment of RRT efficacy challenging.

Our study brings a new insight in the field. By using the propensity technique, we were able to assess the impact of RRT in homogeneous patients who had the same probability of receiving the procedure, somewhat like in a randomized controlled trial. Thus, the risk of biased interpretation of the results was largely minimized. That RRT did not improve ICU patients' survival was unexpected.

A likely explanation for this paradoxical finding is that RRT was in fact initiated too late. Indeed, patients were classified according to the glomerular filtration rate (GFR) criteria of RIFLE (table 6, ESM) whereas increases in serum creatinine often lag behind the true reduction in GFR. Thus, although RRT was in place within 24 hours after reaching maximum RIFLE class in the vast majority of patients, it might well have been initiated at a more advanced stage of renal dysfunction as it seemed at first sight. That patients who received RRT had more coexisting organ failures on RRT initiation than their matched controls on the corresponding time lends support to this hypothesis of delayed AKI diagnosis and RRT. Since initiation of RRT when multiple organ failures are present probably limits its ability to improve patients' outcomes, the utilization of highly sensitive and early diagnostic biomarkers such as cystatin C or neutrophil gelatinase-associated lipocalin (instead of serum creatinine) as triggers for RRT is worth considering for future investigations in the ICU.<sup>16-23</sup>

Even though timing of RRT is undoubtedly a key issue, it must be emphasized that RRT *per se* is potentially harmful. Actually, hemodynamic instability, central venous catheter-related blood stream infections, inflammation and coagulation disorders, which are common



complications of RRT may have outweighed its metabolic benefits, thus also accounting for the absence of beneficial effect in terms of ICU survival.

Despite the use of an original statistical approach minimizing the risk of bias, our study has potential limitations that merit consideration. First, residual confounding cannot be totally ruled out because of the observational design. By applying the propensity technique, however, we dealt with confounding more extensively than in prior reports, in that the assignment of RRT may be considered as “quasi randomized” in the present study. Second, concomitant measures likely to prevent or positively influence the course of renal dysfunction (optimization of hemodynamics and renal perfusion, avoidance of nephrotoxic drugs) were not computed and analyzed. This issue does deserve future prospective evaluations. Third, we encountered the same problem as others:<sup>24, 25</sup> the 6- and 12-hrs urine outputs were not recorded in our database. Therefore, patients were classified according to the GFR criteria only. Patients classified according the GFR criteria seem to be more severely ill and have slightly higher mortality rates than their counterparts classified according to the urine output criteria.<sup>26</sup> <sup>27</sup> Having considered both criteria may have resulted in a different estimation of RRT efficacy. Yet, urine output does not differentiate functional (pre-renal) AKI from organic AKI and new serum or urine biomarkers are probably much more reliable for the early diagnosis of AKI. Fourth, due to the absence of consensual management of AKI in the ICU, inconsistent institutional practices regarding indications, timing and modality of RRT may have been influenced the results of this multicentric study. Finally, data on the long term impact of AKI and RRT, which are also interesting to consider, were not recorded in our database.

In conclusion, our results suggest that current RRT practices may be inappropriate and do not improve ICU patients’ survival. The abovementioned limits stress the need for urgent validation of early and sensitive diagnostic markers and standardization of indications, timing and modality of RRT in order to further evaluate its efficacy in homogeneous populations.

## **CONCISE METHODS**

### *Study Design and Data Source*

We conducted an observational study in a multiple-center database (OUTCOMEREA) from January 1997 to June 2009.

In accordance with French law, the OUTCOMEREA database was declared to the Commission Nationale de l'Informatique et des Libertés. The study was approved by the ethics committee of Clermont-Ferrand, France.

### *Study Population and definitions*

All patients in the database were eligible. Patients with history of chronic kidney disease (with or without complete loss of kidney function), functional renal failure, decision to withhold or withdraw life-sustaining treatments, and RRT for extra-renal indications (e.g., intoxications or cardiogenic shock) were excluded. Among the remaining patients, those with AKI, defined according to the RIFLE criteria,<sup>28</sup> were retained for analysis.

RRT consisted of intermittent hemodialysis or continuous veno-venous hemofiltration / hemodiafiltration. It was considered as early if initiated within 24 hrs after reaching maximum RIFLE class, and as late instead.

### *Data Collection*

The following data were recorded:

- on ICU admission: age, sex, Mc Cabe class,<sup>29</sup> Simplified Acute Physiology Score (SAPS) II,<sup>30</sup> comorbidities assessed according to the Acute Physiology and Chronic

Health Evaluation (APACHE) II definitions,<sup>31</sup> transfer from ward, and admission category,

- during the ICU stay: daily serum creatinine, time from admission to maximum RIFLE class, time to RRT, and daily Sequential Organ Failure Assessment (SOFA) score,<sup>32</sup>
- on ICU discharge: renal status (recovery or need for prolonged renal support), length of ICU stay, and vital status.

### *Endpoints*

The primary endpoint was ICU mortality.

The secondary endpoints were the length of ICU stay, and renal status on ICU discharge.

### *Statistical Analyses*

In the whole cohort, comparisons of patients with and those without RRT were based on chi-square tests for categorical data, and on Student's t-test or Wilcoxon's test for continuous data, as appropriate.

To examine the association of RRT with ICU mortality, we first built a propensity score for RRT to match patients who received RRT to controls who did not despite having the same probability of receiving the procedure. Multivariate conditional regression analysis was then used to adjust for residual confounding factors (namely coexisting organ failures present on RRT initiation or on the corresponding time in controls).

Results of the multivariate model are presented as odds ratios and 95% confidence intervals.

A p value less than .05 was considered to indicate statistical significance. Analyses were computed using the SAS 9.1 software package (SAS Institute, Cary, NC, USA).

## REFERENCES

1. 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* 24:192-198, 1996
2. Liano F, Junco E, Pascual J, Madero R, Verde E: The spectrum of acute renal failure in the intensive care unit compared with that seen in other settings. The Madrid Acute Renal Failure Study Group. *Kidney Int Suppl* 66:S16-24, 1998
3. Mehta RL, Pascual MT, Gruta CG, Zhuang S, Chertow GM: Refining predictive models in critically ill patients with acute renal failure. *J Am Soc Nephrol* 13:1350-1357, 2002
4. Mehta RL, Pascual MT, Soroko S, Savage BR, Himmelfarb J, Ikizler TA, Paganini EP, Chertow GM: Spectrum of acute renal failure in the intensive care unit: the PICARD experience. *Kidney Int* 66:1613-1621, 2004
5. Metnitz PG, Krenn CG, Steltzer H, Lang T, Ploder J, Lenz K, Le Gall JR, Druml W: Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. *Crit Care Med* 30:2051-2058, 2002
6. Greenland S, Neutra R: Control of confounding in the assessment of medical technology. *Int J Epidemiol* 9:361-367, 1980
7. Brochard L, Abroug F, Brenner M, Broccard AF, Danner RL, Ferrer M, Laghi F, Magder S, Papazian L, Pelosi P, Polderman KH: An Official ATS/ERS/ESICM/SCCM/SRLF Statement: Prevention and Management of Acute Renal Failure in the ICU Patient: an international consensus conference in intensive care medicine. *Am J Respir Crit Care Med* 181:1128-1155, 2010
8. Rosenbaum PR, Rubin DB: The central role of the propensity score in observational studies for causal effects. *Biometrika* 70:41-55, 1983
9. Rosenbaum PR, Rubin DB: Reducing bias in observational studies using subclassification on the propensity score. *J Am Stat Assoc* 79:516-524, 1984
10. Augustine JJ, Sandy D, Seifert TH, Paganini EP: A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. *Am J Kidney Dis* 44:1000-1007, 2004
11. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C, Su S: Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 361:1627-1638, 2009
12. Mehta RL, McDonald B, Gabbai FB, Pahl M, Pascual MT, Farkas A, Kaplan RM: A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. *Kidney Int* 60:1154-1163, 2001
13. Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, Finkel K, Kellum JA, Paganini E, Schein RM, Smith MW, Swanson KM, Thompson BT, Vijayan A, Watnick S, Star RA, Peduzzi P: Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 359:7-20, 2008
14. Schiffl H, Lang SM, Fischer R: Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med* 346:305-310, 2002
15. Vinsonneau C, Camus C, Combes A, Costa de Beauregard MA, Klouche K, Boulain T, Pallot JL, Chiche JD, Taupin P, Landais P, Dhainaut JF: Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. *Lancet* 368:379-385, 2006

16. Ahlstrom A, Tallgren M, Peltonen S, Pettila V: Evolution and predictive power of serum cystatin C in acute renal failure. *Clin Nephrol* 62:344-350, 2004
17. Delanaye P, Lambermont B, Chapelle JP, Gielen J, Gerard P, Rorive G: Plasmatic cystatin C for the estimation of glomerular filtration rate in intensive care units. *Intensive Care Med* 30:980-983, 2004
18. Herget-Rosenthal S, Marggraf G, Husing J, Goring F, Pietruck F, Janssen O, Philipp T, Kribben A: Early detection of acute renal failure by serum cystatin C. *Kidney Int* 66:1115-1122, 2004
19. Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, Ruff SM, Zahedi K, Shao M, Bean J, Mori K, Barasch J, Devarajan P: Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet* 365:1231-1238, 2005
20. Nickolas TL, O'Rourke MJ, Yang J, Sise ME, Canetta PA, Barasch N, Buchen C, Khan F, Mori K, Giglio J, Devarajan P, Barasch J: Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. *Ann Intern Med* 148:810-819, 2008
21. Villa P, Jimenez M, Soriano MC, Manzanares J, Casanovas P: Serum cystatin C concentration as a marker of acute renal dysfunction in critically ill patients. *Crit Care* 9:R139-143, 2005
22. Wagener G, Jan M, Kim M, Mori K, Barasch JM, Sladen RN, Lee HT: Association between increases in urinary neutrophil gelatinase-associated lipocalin and acute renal dysfunction after adult cardiac surgery. *Anesthesiology* 105:485-491, 2006
23. Zappitelli M, Washburn KK, Arikian AA, Loftis L, Ma Q, Devarajan P, Parikh CR, Goldstein SL: Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children: a prospective cohort study. *Crit Care* 11:R84, 2007
24. Ostermann M, Chang RW: Acute kidney injury in the intensive care unit according to RIFLE. *Crit Care Med* 35:1837-1843; quiz 1852, 2007
25. Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C: An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. *Crit Care Med* 34:1913-1917, 2006
26. Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, Kellum JA: RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. *Crit Care* 10:R73, 2006
27. Hoste EA, Kellum JA: Acute kidney injury: epidemiology and diagnostic criteria. *Curr Opin Crit Care* 12:531-537, 2006
28. 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* 8:R204-212, 2004
29. McCabe WJ, GG: Gram-negative bacteremia. I. Etiology and ecology. *Arch Intern Med* 110:847-855, 1962
30. Le Gall JR, Lemeshow S, Saulnier F: A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *Jama* 270:2957-2963, 1993
31. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: APACHE II: a severity of disease classification system. *Crit Care Med* 13:818-829, 1985
32. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-

Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 22:707-710, 1996

**Table 1. Baseline characteristics of AKI patients with and without renal replacement therapy (RRT).**

Variable	Patients with RRT	Patients without RRT	<i>P</i> value
	(n = 545)	(n = 2301)	
Age, mean (SD)	61.3 (16.6)	67.6 (15.5)	< 0.0001
Males, no. (%)	363 (66.6)	1309 (59.9)	< 0.0001
SAPS II score, mean (SD)	56.8 (19.2)	48.6 (19.8)	< 0.0001
APACHE II score, mean (SD)	21.4 (7.0)	19.6 (7.1)	< 0.0001
Transfer from ward, no. (%)	291 (53.4)	1072 (46.6)	0.004
McCabe, no. (%)			
1	314 (57.6)	1352 (58.8)	
2	188 (34.5)	771 (33.5)	
3	43 (7.9)	178 (7.7)	0.88
Admission category, no. (%)			
Medical	388 (71.2)	1655 (71.9)	
Scheduled surgery	52 (9.5)	259 (11.3)	
Unscheduled surgery	105 (19.3)	387 (16.8)	0.25
Chronic coexisting conditions, no. (%)			
Cardiac disease	89 (16.3)	420 (18.3)	0.29
Respiratory disease	55 (10.1)	311 (13.5)	0.03
Liver disease	50 (9.2)	128 (5.6)	0.002
Immunodeficiency	104 (19.1)	336 (14.6)	0.01
Uncomplicated diabetes mellitus	63 (11.6)	257 (11.2)	0.79
Complicated diabetes mellitus	30 (5.5)	118 (5.1)	0.72

SAPS, Simplified Acute Physiology Score; APACHE, Acute Physiology and Chronic Health Evaluation.

**Table 2. Differences in serum creatinine on reaching maximum RIFLE class between patients with and without RRT (whole cohort).**

	Patients with RRT	Patients without RRT	<i>P</i> value
<i>R class patients</i>	<i>N</i> = 41	<i>N</i> = 984	
Serum creatinine level (μMol/L)	154 [140-167]	141 [120-159]	0.004
<i>I class patients</i>	<i>N</i> = 110	<i>N</i> = 720	
Serum creatinine level (μMol/L)	205 [184-233]	193 [168-218]	0.002
<i>F class</i>	<i>N</i> = 394	<i>N</i> = 597	
Serum creatinine level (μMol/L)	349 [294-459]	322 [274-424]	0.001

Results are expressed as medians and [interquartile range].



**Table 3. Differences in serum creatinine between matched patients on renal replacement therapy (RRT) initiation (or on the corresponding time in controls).**

	Patients with RRT	Patients without RRT	<i>P</i> value
<i>R class patients</i>	<i>N</i> = 41	<i>N</i> = 170	
Serum creatinine level (μMol/L)	106 [85-144]	106 [81-131]	0.19
<i>I class patients</i>	<i>N</i> = 110	<i>N</i> = 270	
Serum creatinine level (μMol/L)	159 [119-190]	178 [108-200]	0.89
<i>F class patients</i>	<i>N</i> = 371	<i>N</i> = 515	
Serum creatinine level (μMol/L)	271 [193-357]	279 [173-375]	0.51

Results are expressed as medians and [interquartile range].

**Table 4. Differences in modified SOFA score between matched patients on renal replacement therapy (RRT) initiation (or on the corresponding time in controls).**

	Patients with RRT	Patients without RRT	<i>P</i> value
<i>R class</i>	<i>N</i> = 41	<i>N</i> = 170	
mSOFA, median [interquartile range]	9 [7-12]	3 [1-5]	< 0.0001
<i>I class</i>	<i>N</i> = 110	<i>N</i> = 270	
mSOFA, median [interquartile range]	8 [6-11]	4 [2-6]	< 0.0001
<i>F class</i>	<i>N</i> = 371	<i>N</i> = 515	
mSOFA, median [interquartile range]	7 [4-9]	4 [2-6]	< 0.0001

Results are expressed as medians and [interquartile range].

SOFA, Sequential Organ Failure Assessment; mSOFA = SOFA – specific renal component.

**Table 5. Independent association of renal replacement therapy (RRT) with intensive care unit (ICU) mortality according to the maximum RIFLE class reached during the ICU stay (matched patients).**

	OR	95% CI	<i>P</i> value
<i>R class</i>			
No RRT	1	-	-
RRT (whatever the timing)	1.59	0.73-3.44	0.24
Early* RRT	1.64	0.68-3.97	0.27
Late** RRT	1.44	0.35-5.89	0.61
<i>I class</i>			
No RRT	1	-	-
RRT (whatever the timing)	1.32	0.65-2.67	0.45
Early* RRT	1.31	0.61-2.82	0.49
Late** RRT	1.33	0.33-5.35	0.69
<i>F class</i>			
No RRT	1	-	-
RRT (whatever the timing)	2.42	1.52-3.86	< 0.001
Early* RRT	1.54	0.86-2.75	0.14
Late** RRT	5.90	2.36-14.74	< 0.001

OR, odds ratio; CI, confidence interval.

\* initiated within 24 hrs after reaching maximum RIFLE class.

\*\* initiated more than 24 hrs after reaching maximum RIFLE class.

## **ELECTRONIC SUPPLEMENTARY MATERIAL**

### **METHODS**

#### *Study Design and Data Source*

We conducted an observational study in a multiple-center database (OUTCOMEREA) from January 1997 to June 2009. The database, which receives information from 13 French intensive care units (ICU), is designed to record daily disease severity scores and the occurrence of iatrogenic events. Methods of data collection and quality of the database have been described in details elsewhere.<sup>1</sup> Briefly a large set of data on a random sample of patients older than 16 years with ICU stays longer than 24 h was prospectively collected by the senior physicians of the participating ICUs and entered into the database each year. Participating ICUs could choose between two sampling methods: consecutive admitted patients in randomized beds or consecutive admitted patients in a randomized month. The quality control procedure involved multiple automatic checking of internal consistency and biennial audits. Moreover, a one-day data-capture training course is held once a year for all OutcomeRea investigators and study monitors. Senior physicians and participating centers are listed in the appendix.

In accordance with French law, the OUTCOMEREA database was declared to the Commission Nationale de l'Informatique et des Libertés. The study was approved by the ethics committee of Clermont-Ferrand, France. Because routine collection of data entered into the database did not modify patients' management in any way, and statistical analyses were processed anonymously, informed consent for participation in the study was waived.

#### *Study Population and definitions*

All patients in the database were eligible. Patients with history of chronic kidney disease (with or without complete loss of kidney function), functional (pre-renal) renal failure, decision to withhold or withdraw life-sustaining treatments, and renal replacement therapy (RRT) for extra-renal indications (e.g., intoxications or cardiogenic shock) were excluded. Among the remaining patients, those in whom acute kidney injury (AKI) occurred were retained for analysis.

AKI was defined according to the RIFLE criteria,<sup>2</sup> and patients were classified according to the maximum RIFLE class (Risk, Injury or Failure) reached during their ICU stay. Since the 6- and 12-hrs urine outputs were not recorded in the database, we used the glomerular filtration rate (GFR) only. The GFR criteria were determined according to changes in serum creatinine from baseline values. Since AKI may be present on ICU admission in a high proportion of patients, we chose to assess baseline creatinine values using the Modification of Diet in Renal Disease (MDRD) equation. As recommended by the Acute Dialysis Quality Initiative Group, a normal GFR of 75 ml/min/1.73 m<sup>2</sup> before ICU admission was assumed.<sup>2</sup>

RRT consisted of intermittent hemodialysis or continuous veno-venous hemofiltration / hemodiafiltration. RRT was considered as early if initiated within 24 hrs after reaching maximum RIFLE class, and was considered as late instead.

For patients who were admitted more than once to the ICU, only the first ICU stay was included in the analysis.

### *Data Collection*

The following data were recorded:

- on ICU admission: age, sex, McCabe class (class 1, no fatal underlying disease; class 2, underlying disease fatal within 5 years; class 3, underlying disease fatal within 1 year), Simplified Acute Physiology Score (SAPS) II, comorbidities assessed according

to the Acute Physiology and Chronic Health Evaluation (APACHE) II definitions, transfer from ward (defined as a stay in an acute-bed ward  $\geq$  24 hrs immediately before ICU admission), and admission category (medical, scheduled surgery, or unscheduled surgery),

- during the ICU stay: daily serum creatinine, time from admission to maximum RIFLE class, time to RRT, and daily Sequential Organ Failure Assessment (SOFA) score,
- on ICU discharge: renal status (recovery or need for prolonged renal support), length of ICU stay, and vital status.

### *Endpoints*

The primary endpoints was ICU mortality.

The secondary endpoints were the length of ICU stay, and renal status on ICU discharge.

### *Statistical Analyses*

In the whole cohort, comparisons of patients with and those without RRT were based on chi-square tests for categorical data, and on Student's t-test or Wilcoxon's test for continuous data, as appropriate.

Since RRT was not randomly assigned in the study population, treatment selection bias and potential confounding were accounted for by developing a propensity score for RRT. The rationale and methods underlying the use of a propensity score for a proposed causal exposure variable have been previously described.<sup>3</sup> The propensity score for RRT was determined using a multivariate logistic regression analysis. As recommended, variables introduced in the propensity regression (SAPS II score and RIFLE class) were related to both outcome and treatment exposure to reduce the risk of bias and the variance in the estimation of treatment effect.<sup>4,5</sup> Since there are no clear indications for RRT, patients with an equal propensity score

(ie, with the same probability of receiving RRT) may or may not have actually received RRT, as though RRT was randomized.

To examine the association of RRT with ICU mortality, we first matched patients who received RRT during their ICU stay to other AKI patients who did not on the basis of the propensity score that we built. Specifically, we sought to match each patient with RRT up to 3 controls who had the closest propensity score (within 0.05 on a scale of 0 to 1). We also imposed that the time from maximum RIFLE class to RRT initiation in patients with RRT be less or equal than the time from maximum RIFLE class to ICU discharge in their respective controls. Multivariate analysis was then used to adjust for residual confounding factors (namely coexisting organ failures present on RRT initiation or on the corresponding time in controls).

Results of the multivariate model are presented as odds ratios and 95% confidence intervals.

A *p* value less than .05 was considered significant. Analyses were computed using the SAS 9.1 (SAS Institute, Cary, NC, USA) and the free R software packages.

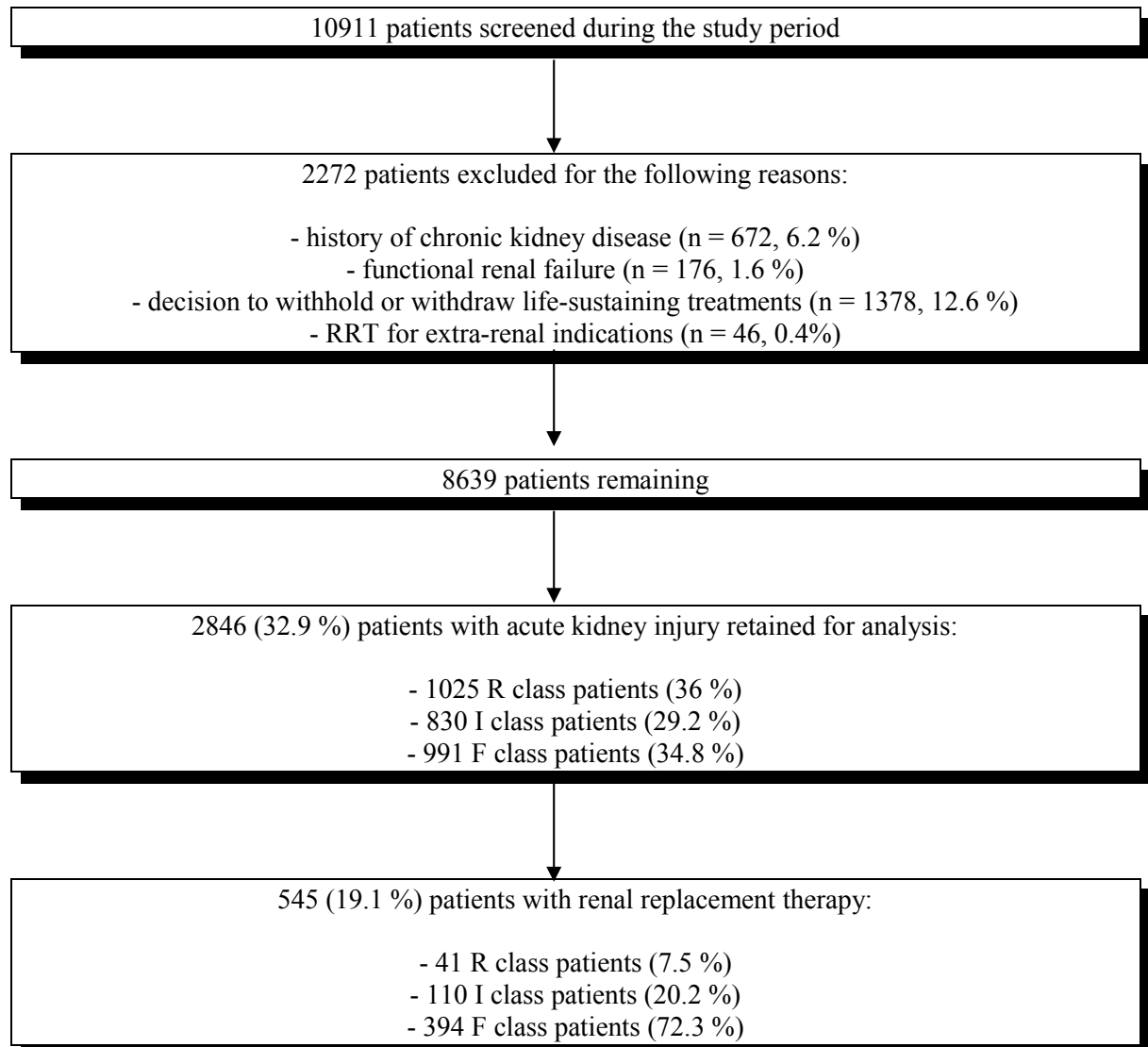
## REFERENCES

1. Clec'h C, Alberti C, Vincent F, Garrouste-Orgeas M, de Lassence A, Toledano D, Azoulay E, Adrie C, Jamali S, Zaccaria I, Cohen Y, Timsit JF: Tracheostomy does not improve the outcome of patients requiring prolonged mechanical ventilation: a propensity analysis. *Crit Care Med*, 35:132-138, 2007
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*, 8:R204-212, 2004
3. Joffe MM, Rosenbaum PR: Invited commentary: propensity scores. *Am J Epidemiol*, 150:327-333, 1999
4. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T: Variable selection for propensity score models. *Am J Epidemiol*, 163:1149-1156, 2006
5. Rubin DB, Thomas N: Matching using estimated propensity scores: relating theory to practice. *Biometrics*, 52:249-264, 1996



## RESULTS

**Figure 1. Study flow chart**



**Table 1. Baseline characteristics of RIFLE R class patients with and without renal replacement therapy (RRT).**

Variable	Patients with RRT	Patients without RRT	<i>P</i> value
	(n = 41)	(n = 984)	
Age, mean (SD)	59.2 (17.0)	67.9 (15.6)	< 0.001
Males, no. (%)	32 (78.1)	556 (56.5)	0.006
SAPS II score, mean (SD)	57.6 (20.4)	44.7 (17.1)	< 0.0001
APACHE II score, mean (SD)	22.3 (6.9)	17.8 (6.5)	< 0.0001
Transfer from ward, no. (%)	19 (46.3)	458 (46.6)	0.98
McCabe, no. (%)			
1	17 (41.5)	591 (60.1)	
2	18 (43.9)	324 (32.9)	
3	6 (14.6)	69 (7.0)	0.03
Admission category, no. (%)			
Medical	32 (78.1)	722 (73.4)	
Scheduled surgery	4 (9.8)	126 (12.8)	
Unscheduled surgery	5 (12.2)	136 (13.8)	0.79
Chronic coexisting conditions, no. (%)			
Cardiac disease	11 (26.8)	174 (17.7)	0.14
Respiratory disease	7 (17.1)	158 (16.1)	0.86
Liver disease	5 (12.2)	56 (5.7)	0.09
Immunodeficiency	8 (19.5)	135 (13.7)	0.29
Uncomplicated diabetes mellitus	8 (19.5)	117 (11.9)	0.15
Complicated diabetes mellitus	0 (0)	45 (4.6)	0.25

SAPS, Simplified Acute Physiology Score; APACHE, Acute Physiology and Chronic Health Evaluation.

**Table 2. Baseline characteristics of RIFLE I class patients with and without renal replacement therapy (RRT).**

Variable	Patients with RRT	Patients without RRT	<i>P</i> value
	(n = 110)	(n = 720)	
Age, mean (SD)	61.6 (17.0)	67.5 (15.3)	< 0.001
Males, no. (%)	74 (67.3)	428 (59.4)	0.12
SAPS II score, mean (SD)	61.9 (21.2)	50.4 (20.8)	< 0.0001
APACHE II score, mean (SD)	21.8 (6.9)	20.5 (7.2)	0.07
Transfer from ward, no. (%)	58 (52.7)	329 (45.7)	0.17
McCabe, no. (%)			
1	60 (54.6)	416 (57.8)	
2	42 (38.2)	248 (34.4)	
3	8 (7.2)	56 (7.8)	0.75
Admission category, no. (%)			
Medical	85 (77.3)	507 (70.4)	
Scheduled surgery	5 (4.5)	80 (11.1)	
Unscheduled surgery	20 (18.2)	133 (18.5)	0.10
Chronic coexisting conditions, no. (%)			
Cardiac disease	16 (14.6)	147 (20.4)	0.15
Respiratory disease	10 (9.1)	91 (12.6)	0.29
Liver disease	16 (14.6)	43 (6.0)	0.004
Immunodeficiency	28 (25.5)	109 (15.7)	0.09
Uncomplicated diabetes mellitus	10 (9.1)	80 (11.1)	0.52
Complicated diabetes mellitus	3 (2.7)	37 (5.1)	0.27

SAPS, Simplified Acute Physiology Score; APACHE, Acute Physiology and Chronic Health Evaluation.

**Table 3. Baseline characteristics of RIFLE F class patients with and without renal replacement therapy (RRT).**

Variable	Patients with RRT	Patients without RRT	<i>P</i> value
	(n = 394)	(n = 597)	
Age, mean (SD)	61.4 (16.4)	67.3 (15.4)	< 0.0001
Males, no. (%)	257 (65.2)	325 (54.4)	< 0.001
SAPS II score, mean (SD)	55.3 (18.2)	52.8 (21.6)	0.05
APACHE II score, mean (SD)	21.3 (7.0)	21.5 (7.2)	0.53
Transfer from ward, no. (%)	214 (54.3)	285 (47.7)	0.04
McCabe, no. (%)			
1	237 (60.2)	345 (57.8)	
2	128 (32.5)	199 (33.3)	
3	29 (7.3)	53 (8.9)	0.53
Admission category, no. (%)			
Medical	271 (68.8)	426 (71.3)	
Scheduled surgery	43 (10.9)	53 (8.9)	
Unscheduled surgery	80 (20.3)	118 (19.8)	0.63
Chronic coexisting conditions, no. (%)			
Cardiac disease	62 (15.7)	99 (16.6)	0.72
Respiratory disease	38 (9.6)	62 (10.4)	0.71
Liver disease	29 (7.4)	29 (4.9)	0.004
Immunodeficiency	28 (25.5)	109 (15.7)	0.11
Uncomplicated diabetes mellitus	45 (11.4)	60 (10.1)	0.49
Complicated diabetes mellitus	27 (6.9)	36 (6.0)	0.61

SAPS, Simplified Acute Physiology Score; APACHE, Acute Physiology and Chronic Health Evaluation.

**Table 4. Lengths of intensive care unit stay after reaching maximum RIFLE class in patients with and without renal replacement therapy (RRT).**

	Patients with RRT	Patients without RRT	<i>P</i> value
<i>All patients</i>	<i>N</i> = 545	<i>N</i> = 2301	
Days, median [interquartile range]	13 [7-26]	6 [3-11]	< 0.0001
<i>R class patients</i>	<i>N</i> = 41	<i>N</i> = 984	
Days, median [interquartile range]	12 [4-18]	5 [3-10]	0.001
<i>I class patients</i>	<i>N</i> = 110	<i>N</i> = 720	
Days, median [interquartile range]	11 [6-22]	6 [3-11]	< 0.0001
<i>F class patients</i>	<i>N</i> = 394	<i>N</i> = 597	
Days, median [interquartile range]	14 [7-27]	6 [3-11]	< 0.0001

**Table 5. Lengths of intensive care unit stay after reaching maximum RIFLE class in non survivors with and without renal replacement therapy (RRT).**

	Patients with RRT	Patients without RRT	<i>P</i> value
<i>All patients</i>	<i>N</i> = 207	<i>N</i> = 403	
Days, median [interquartile range]	10 [5-19]	3 [2-8]	< 0.0001
<i>R class patients</i>	<i>N</i> = 19	<i>N</i> = 101	
Days, median [interquartile range]	9 [3-16]	4 [2-10]	0.02
<i>I class patients</i>	<i>N</i> = 59	<i>N</i> = 170	
Days, median [interquartile range]	9 [4-21]	3 [2-8]	< 0.0001
<i>F class patients</i>	<i>N</i> = 129	<i>N</i> = 132	
Days, median [interquartile range]	11 [6-19]	3 [2-7]	< 0.0001

**Table 6. RIFLE classification.**

RIFLE class	GFR criteria	UO criteria
Risk	Increase in serum creatinine $\geq 1.5$ X baseline or decrease in GFR $\geq 25$ %	$< 0.5$ ml/kg/h for $\geq 6$ hrs
Injury	Increase in serum creatinine $\geq 2$ X baseline or decrease in GFR $\geq 50$ %	$< 0.5$ ml/kg/h for $\geq 12$ hrs
Failure	Increase in serum creatinine $\geq 3$ X baseline or decrease in GFR $\geq 75$ % or serum creatinine $\geq 350$ $\mu\text{mol/L}$ with an acute rise of at least $44$ $\mu\text{mol/L}$	$< 0.3$ ml/kg/h for $\geq 24$ hrs or anuria $\geq 12$ hrs
Loss	Complete loss of kidney function $> 4$ weeks	
End-stage kidney disease	Need for RRT $> 3$ months	

GFR, glomerular filtration rate; UO, urine output; RRT, renal replacement therapy.

# **Troisième partie**

*Cas particulier des  
produits de contraste iodés*



### III.1 Considérations épidémiologiques

Les connaissances actuelles sur l'atteinte rénale aiguë induite par les produits de contraste iodés proviennent essentiellement des études réalisées dans les domaines de la cardiologie et de la radiologie. Comme pour l'AKI en général, l'interprétation des données épidémiologiques se heurte à l'obstacle de l'absence de critères diagnostiques consensuels et de l'hétérogénéité des patients. Ainsi, en fonction de la définition choisie et de la population étudiée, l'incidence varie de moins de 5 % à plus de 50 %<sup>6, 7, 47-51</sup> et la mortalité, elle, varie de 14 % à 34 %<sup>49, 52-54</sup> avec des pics à 60 %<sup>6</sup> pour les patients nécessitant une suppléance rénale. Point remarquable, le risque accru de mortalité et d'effets secondaires au sens large semble persister à long terme.<sup>55-57</sup>

Se basant sur ces considérations, les radiologues refusent fréquemment de pratiquer des examens tomodensitométriques avec injection de produit de contraste chez les patients dont la fonction rénale n'est pas connue, ou, a fortiori, altérée. Dans les situations où la précocité du diagnostic et du traitement conditionne le pronostic, cette attitude pose problème, alors même qu'elle n'est pas supportée par les recommandations d'experts qui précisent clairement que dans un contexte d'urgence, le rapport bénéfices / risques est favorable à l'imagerie et qu'il n'est alors pas licite d'attendre la mesure de la créatininémie ou du débit de filtration glomérulaire.<sup>58</sup> Les études récentes montrant l'effet protecteur des nouveaux produits de contraste iso et hypo-osmolaires et des mesures préventives<sup>59-66</sup> ainsi que la diminution marquée de l'incidence et possiblement de la mortalité de l'atteinte rénale aiguë induite par les produits de contraste iodés sur la dernière décennie<sup>67, 68</sup> sont autant d'arguments supplémentaires à opposer aux radiologues. Néanmoins, les échanges avec les radiologues ont le mérite de tenir en alerte les prescripteurs qui auraient tendance à sous-estimer un problème aux conséquences potentielles sévères.

Paradoxalement, alors que les patients de réanimation sont particulièrement exposés au risque d'atteinte rénale aiguë induite par les produits de contraste iodés, du fait de la fréquence des examens d'imagerie ainsi que des nombreux facteurs de risque de dysfonction rénale coexistants, la littérature les concernant est très pauvre tant quantitativement que qualitativement.<sup>6, 7</sup> De nouvelles investigations sur l'atteinte rénale aiguë induite par les produits de contraste iodés spécifiques aux patients de réanimation apparaissent donc indispensables pour d'une part évaluer précisément l'incidence de cette pathologie, d'autre part en identifier des facteurs prédictifs de survenue (afin de mieux cibler les patients à risque le plus susceptibles de bénéficier de mesures préventives), et, enfin, en évaluer l'impact sur la nécessité de recourir à l'EER et sur la mortalité en réanimation.

## III.2 Considérations méthodologiques

Plusieurs modèles permettant d'identifier des facteurs pronostiques de mortalité en réanimation sont actuellement disponibles. Le plus employé dans la littérature est la régression logistique, suivie, d'assez loin, par le modèle de Cox. L'utilisation des modèles à risques compétitifs, de développement plus récent et de mise en œuvre plus complexe, reste à ce jour marginale.<sup>26, 27</sup>

Dans l'étude qui suit, mise en place en début de thèse, c'est la régression logistique qui a été choisie pour évaluer l'impact pronostique de l'atteinte rénale aiguë liée aux produits de contraste iodés. Les modèles plus élaborés ont été explorés ultérieurement.

Chacun de ses modèles présente des avantages et des inconvénients. Le propos ici n'est pas de revenir en détails sur leurs principes fondamentaux, thème précédemment abordé, mais de préciser les termes du débat opposant les partisans des modèles de survie (modèle de Cox et modèles à risques compétitifs) à ceux de la régression logistique. Le point de vue des premiers a été défendu dans le chapitre I.2 : le caractère temps-dépendant de l'événement d'intérêt et de l'exposition aux différents facteurs de risque impose pour eux le recours aux modèles de survie et plus particulièrement aux modèles à risques compétitifs dans la mesure où l'hypothèse d'indépendance de l'événement d'intérêt par rapport à la censure n'est habituellement pas vérifiée. Exposons à présent le point de vue des seconds.<sup>69</sup> A leurs yeux, les principaux arguments devant faire préférer la régression logistique aux modèles de survie sont de trois ordres. Premièrement, malgré l'intégration de la censure droite, aucun des modèles de survie ne résout véritablement le problème des décès non observés, c'est-à-dire des décès survenant après la fin de la période d'observation, que la censure soit considérée informative ou non informative. La régression fait finalement l'hypothèse que le décès ne surviendra pas après la censure, le modèle de Cox que celui-ci surviendra à la même vitesse que chez les individus non censurés. La différence majeure entre les 2 types de modèle est que

l'un (régression logistique) modélise la survenue d'un événement, alors que l'autre (modèle de Cox) modélise la vitesse de survenue de l'évènement. Le modèle de Cox n'apporte donc de bénéfice majeur que si c'est bien la vitesse d'acquisition de l'évènement qui nous intéresse et si la censure est décidée a priori et indépendamment de la date de survenue de l'évènement. Ainsi, les modèles de survie peuvent mettre en évidence une prolongation de la survie sans pour autant influencer le statut à la survenue de la censure. Par exemple, on peut imaginer un traitement retardant la survenue du décès de quelques jours mais n'influençant pas la survie à 1 mois.<sup>70</sup> Dans ce cas le bénéfice « statistique » ne correspond pas au bénéfice « clinique ». Deuxièmement, les estimateurs produits par la régression logistique et ceux produits par les modèles de survie sont parfois très proches, notamment lorsque la durée de suivi est courte et que l'évènement d'intérêt est rare.<sup>71-73</sup> Il faut cependant souligner que l'odds ratio directement tiré des modèles de régression logistique est un mauvais reflet du risque relatif qui est vraiment ce qui nous intéresse quand l'évènement survient fréquemment. Troisièmement, enfin, la régression logistique est un modèle relativement simple à concevoir et à utiliser et aboutissant plus simplement à une probabilité prédite de survenue de l'évènement, ce qui en facilite la diffusion, la compréhension et l'application par la communauté médicale.

### **III.3 Application**

Cet article se propose d'évaluer l'incidence, les facteurs favorisants et l'impact sur la mortalité en réanimation de la toxicité des produits de contraste iodés. Il a été soumis pour publication à « *Intensive Care Medicine* ».

Il souligne l'incidence élevée (souvent sous-estimée en pratique quotidienne) et le pronostic péjoratif de l'atteinte rénale aiguë liée aux produits de contraste iodés. Sans surprise, même si cela n'avait jusque là pas été formellement démontré, cette complication survient essentiellement sur un terrain prédisposé (coexistence d'autres facteurs de risque de dysfonction rénale). L'absence de « réversibilité » par l'EER, en revanche, est un résultat marquant qui mérite d'être porté à la réflexion des cliniciens.

**Contrast-induced acute kidney injury after computed tomography: a common and severe complication in critically ill patients.**

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## **Abstract**

*Purpose:* Data on contrast-induced acute kidney injury (CIAKI) in the intensive care unit (ICU) are very scarce, despite computed tomography with iodinated contrast media being widely used. Our aim was to assess the incidence of CIAKI in critically ill patients, and its impact in terms of need for renal replacement therapy (RRT) and ICU mortality.

*Methods:* We conducted a retrospective study in the ICU of the Avicenne teaching hospital (Bobigny, France) between September 2006 and December 2008. Were included adult patients without pre-existing renal disease, and not on RRT before computed tomography. CIAKI was defined as either a relative increment in serum creatinine of  $\geq 25\%$  or an absolute increment in serum creatinine of  $\geq 0.3$  mg/dL. The primary endpoints were the incidence of CIAKI and the need for RRT (assessed within 48 hours after the first administration of iodinated contrast media), and ICU mortality.

*Results:* Data from 143 patients were analyzed. CIAKI occurred in 24 patients (16.8%), of whom 7 (29.2%) required RRT. ICU mortality was significantly higher in patients with than in those without CIAKI (50% vs 21%,  $p = 0.004$ ). In multivariate analysis, CIAKI remained independently associated with ICU mortality. Remarkably, RRT had no obvious positive effect on patients' outcome.

*Conclusions:* CIAKI appears to be a common complication leading to significant morbidity and mortality. Accordingly, administration of iodinated contrast media for computed tomography should be considered as a high-risk procedure in ICU patients and not as a routine innocuous practice.

Key words: acute kidney injury, iodinated contrast media, intensive care unit, prognosis.



## **Introduction**

The risk of contrast-induced acute kidney injury (CIAKI) associated with the growing use of imaging and interventional radiographic procedures is a major concern to cardiologists, radiologists and intensivists. Actually, CIAKI has been shown to lead to significant morbidity and mortality, even though its incidence and impact vary widely according to the definition used [1-10].

Noteworthy, data on CIAKI in the intensive care unit (ICU) setting are very scarce [3, 8, 11], despite computed tomography with iodinated contrast media being a common procedure in critically ill patients. Whether the benefits of contrast media administration in terms of improved diagnostic accuracy outweigh the risk of CIAKI remains a topic of debate. Early imaging and subsequent appropriate treatment are of utmost importance but the initial benefit may be further offset if CIAKI occurs.

Based on these considerations, radiologists are often reluctant to administer contrast media in patients with pre-existing renal dysfunction or in patients, whose renal function is unknown. This attitude, which is not always shared by intensivists, is supported neither by recommendations of the Contrast-Induced Nephropathy Consensus Working Panel [12] nor by recent data suggesting that the incidence of CIAKI is low, and that CIAKI has only a minor impact, especially after computed tomography [13, 14]. Nonetheless, critically ill patients often present multiple risk factors for renal dysfunction and may be at a very high risk of CIAKI [15, 16]. Since the benefit/risk ratio of contrast media administration appears essential to determine, precise data on CIAKI in the ICU are required.

The aim of this study was two-folded: 1/ to assess the incidence of CIAKI in a general ICU population, and 2/ to test whether CIAKI is associated with increased need for renal replacement therapy (RRT) and ICU mortality.

## **Methods**

### *Study design, patients, and definition*

This retrospective study was carried out in the medical-surgical ICU of the Avicenne teaching hospital (Bobigny, France).

All adult patients who received intravenous iodinated contrast media for computed tomography between September 2006 and December 2008 were eligible. The incidence of CIAKI was assessed within 48 hours after the first administration of iodinated contrast media using two non-mutually exclusive definitions: 1) a relative increment in serum creatinine of  $\geq 25\%$  from baseline, as in many prior reports [17], and 2) an absolute increment in serum creatinine of  $\geq 0.3$  mg/dL (26  $\mu$ mol/L) from baseline, as suggested by the Acute Kidney Injury Network [18]. Exclusion criteria were: history of chronic kidney disease, RRT before administration of iodinated contrast media, and re-administration of iodinated contrast media within 48 hours. For patients who were admitted more than once to the ICU, only the first ICU stay was included in the analysis.

The decision to perform a computed tomography with iodinated contrast media was left at the attending physicians' discretion. During the whole study period, iso-osmolar media only were used. There were no written protocols for either CIAKI prevention or dosing of iodinated contrast. No patient received prophylactic RRT.

Since the study implied no change in patients' management and data were anonymously processed, the need for informed consent was waived.

### *Data collection*

For each patient, the following variables were collected:

- Baseline characteristics: age, gender, SAPS II score, Mc Cabe class (class 1, no fatal underlying disease; class 2, underlying disease fatal within 5 years; class 3, underlying disease fatal within 1 year), admission category (medical, scheduled surgery, or unscheduled surgery), and comorbidities (diabetes mellitus, myeloma and other chronic coexisting conditions defined according to the Knaus criteria [19]),
- Serum creatinine values measured on the computed tomography day before administration of iodinated contrast media, and 24 hours and 48 hours thereafter,
- Additional risk factors for renal dysfunction occurring within 48 hours before and after administration of iodinated contrast media: sepsis, hemodynamic failure and prescription of nephrotoxic drugs,
- Presence or absence of preventive measures (*N*-acetylcysteine or isotonic crystalloids), and
- Impact of CIAKI: need for RRT within 48 hours after the first administration of iodinated contrast media, ICU mortality, length of ICU stay and persistent need for renal support on ICU discharge.

### *Endpoints*

The primary endpoints were the incidence of CIAKI, and its impact on the need for RRT and ICU mortality.

The secondary endpoints were the length of ICU stay, and persistent need for renal support on ICU discharge.

### *Statistical analyses*

Comparisons between patients with and those without CIAKI were based on the Fischer's exact test for categorical variables and on the Wilcoxon's test for continuous variables.

The independent effect of CIAKI on ICU mortality was assessed through a logistic regression model. Specifically, we adjusted for patients' baseline severity reflected by the SAPS II score and for organ dysfunctions before administration of iodinated contrast media reflected by the non-renal SOFA score (SOFA - renal component). The goodness of fit and the discrimination of the model were determined by the Hosmer-Lemeshow statistic and the *c* statistic (area under the curve), respectively. Results are shown as adjusted odds ratios with their 95% confidence intervals.

All *p* values were two-tailed, and  $p < .05$  was considered significant.

Statistical analyses were performed using a statistical software package (SAS, version 9.1; SAS Institute; Cary, NC).

## **Results**

### *Patients*

Over the study period, 1639 patients were screened. A computed tomography was performed in 256 (15.6%) patients, of whom 194 (75.8%) received iodinated contrast media. Forty patients were excluded for the following reasons (history of chronic kidney disease,  $n = 5$ ; RRT before administration of contrast media,  $n = 25$ ; and re-administration of iodinated contrast media within 48 hours,  $n = 10$ ). In 11 cases, the patient's data file was incomplete. Finally, 143 patients were retained for analysis.

### *Incidence of CIAKI*

CIAKI occurred in 24/143 (16.8%) patients. Whereas there was no difference in serum creatinine before computed tomography between patients with and those without CIAKI, CIAKI patients had more risk factors for renal dysfunction within 48 hours before administration of iodinated contrast media (table 1).

#### *Association of CIAKI with renal replacement therapy*

RRT was initiated in 7/24 (29.2%) CIAKI patients with a median time of 1 day (interquartile range: 0-3). Over 80% of these patients were exposed to new risk factors for renal dysfunction. CIAKI patients who received RRT had similar SAPS II scores and serum creatinine before computed tomography as CIAKI patients who did not receive RRT but had more failing organs before computed tomography and were more likely to die in the ICU, although statistical significance was not reached (table 2). In the two surviving CIAKI patients who received RRT, renal function recovered on ICU discharge.

#### *Association of CIAKI with mortality*

Patients with CIAKI had a significantly higher crude mortality rate than patients without CIAKI (50% vs 21%,  $p = 0.004$ ). After adjustment for patients' severity, CIAKI remained an independent risk factor for ICU mortality (table 3).

#### *Association of CIAKI with length of ICU stay*

Patients with and those without CIAKI had similar lengths of ICU stay (median in days, [interquartile range]: 8 [4-22] vs 8 [6-23],  $p = 0.66$ ).

## **Discussion**

While the risk of CIAKI among critically ill patients is a major concern in everyday practice, the current literature is paradoxically scarce [17]. Very few studies in the ICU population have been carried out so far, with inconsistent results. In 2006, Haveman et al. [3] found that the incidence of CIAKI (defined as an increment in serum creatinine of  $> 0.5 \text{ mg/dL}$  - $44 \mu\text{mol/L}$ - within 48 hrs) was 1.4% in surgical patients, with a further 3.5% receiving RRT after computed tomography. Huber et al. reported a similarly low incidence using the same definition in patients receiving theophylline prophylaxis [11]. On the other hand, Polena et al. observed an incidence of 18% using a more sensitive definition of CIAKI (increment in serum creatinine of  $> 25\%$ ) in patients without pre-existing renal disease [8]. It was unclear whether CIAKI was responsible for increased ICU mortality or need for RRT in any of these studies. Contrarily, our work strongly suggests that CIAKI leads to significant morbidity and mortality. Thus, administration of iodinated contrast media should not be viewed as a routine innocuous practice but rather as a high-risk procedure in ICU patients.

Some important findings merit consideration. First the incidence of CIAKI was much higher than previously reported [3, 11]. This was probably due to the choice of sensitive definition criteria. Had we chosen less sensitive criteria, the incidence would have been lower (with conversely higher mortality, however). Another explanation is the low rate of preventive measures, at least partly ascribable to the fact that computed tomography was required in emergency most of the time. Second, in keeping with prior studies, we showed that even a slight increase in serum creatinine impaired patients' outcomes [20], and that patients with pre-existing risk factors for renal dysfunction were the most likely to develop CIAKI [3]. Third, we found that RRT had no or little protective effect once CIAKI had occurred. CIAKI patients who required RRT had more failing organs than their counterparts without RRT and tended to die more frequently in the ICU. Accordingly, the technical possibility to put patients on RRT must not be used as an argument to "force" radiologists to administer iodinated

contrast media. Fourth, although most patients had several coexisting causes of renal dysfunction, and no direct link between administration of iodinated contrast media and subsequent renal dysfunction or need for RRT could be demonstrated, our results emphasize that iodinated contrast media are all the more harmful to the kidney, as patients are exposed to other risk factors for nephrotoxicity and have multiple organ failures. Finally, CIAKI was associated with a significantly increased risk of ICU death, even after adjustment for patients' severity (assessed at baseline and before computed tomography).

Based on these issues, administration of iodinated contrast media should be considered with caution in ICU patients and expected benefits of the procedure should be clearly settled beforehand.

Despite bringing a new insight into the field of CIAKI, our study has potential limitations pertaining to its monocentric and retrospective design. The incidence of CIAKI varying according to the definition used and being undoubtedly influenced by local practices regarding prevention and RRT, the external validity of our monocentric evaluation is difficult to ascertain. It must be noticed, however, that any study will encounter the same problem until consensual definition criteria for CIAKI and indications for RRT are determined and widely accepted. As to the retrospective design, it may have led to selection and measurement biases. Yet, patients who received iodinated contrast media were easily identified, the proportion of incomplete files was low, and data used for analysis were highly reproducible. The retrospective design also refrained from evaluating the true benefit/risk ratio of the procedure. Actually, precise indications and findings of computed tomographies as well as subsequent therapeutic changes were uneasy to extract from patients' files and would have been hazardous to analyze. The doses of contrast media administered to patients, which may play an important role [17], were difficult to gather retrospectively as well. Finally, the impact of

repeated administrations of iodinated contrast media was not assessed because of the many confounding factors, but deserves further investigations.

In conclusion, CIAKI after computed tomography was a common and severe complication in our cohort of patients. Coexisting causes of renal dysfunction were frequent, related mortality was significant, and, remarkably, RRT had no obvious positive effect. Therefore, administration of iodinated contrast media should be considered as a high-risk procedure in ICU patients and not as a routine innocuous practice, all the more as CIAKI may also impair long-term prognosis [21]. Further prospective, multicentric studies are warranted to confirm our results.



## References

1. Cigarroa RG, Lange RA, Williams RH and Hillis LD (1989) Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. *Am J Med* 86:649-652
2. Gruberg L, Mintz GS, Mehran R, Gangas G, Lansky AJ, Kent KM, Pichard AD, Satler LF and Leon MB (2000) The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. *J Am Coll Cardiol* 36:1542-1548
3. Haveman JW, Gansevoort RT, Bongaerts AH and Nijsten MW (2006) Low incidence of nephropathy in surgical ICU patients receiving intravenous contrast: a retrospective analysis. *Intensive Care Med* 32:1199-1205
4. Lautin EM, Freeman NJ, Schoenfeld AH, Bakal CW, Haramati N, Friedman AC, Lautin JL, Braha S, Kadish EG, Sprayregen S and et al. (1991) Radiocontrast-associated renal dysfunction: incidence and risk factors. *AJR Am J Roentgenol* 157:49-58
5. Levy EM, Viscoli CM and Horwitz RI (1996) The effect of acute renal failure on mortality. A cohort analysis. *Jama* 275:1489-1494
6. McCullough PA, Wolyn R, Rocher LL, Levin RN and O'Neill WW (1997) Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med* 103:368-375
7. Parfrey PS, Griffiths SM, Barrett BJ, Paul MD, Genge M, Withers J, Farid N and McManamon PJ (1989) Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. *N Engl J Med* 320:143-149

8. Polena S, Yang S, Alam R, Gricius J, Gupta JR, Badalova N, Chuang P, Gintautas J and Conetta R (2005) Nephropathy in critically ill patients without preexisting renal disease. *Proc West Pharmacol Soc* 48:134-135
9. Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, Singh M, Bell MR, Barsness GW, Mathew V, Garratt KN and Holmes DR, Jr. (2002) Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 105:2259-2264
10. Weisberg LS, Kurnik PB and Kurnik BR (1994) Risk of radiocontrast nephropathy in patients with and without diabetes mellitus. *Kidney Int* 45:259-265
11. Huber W, Jeschke B, Page M, Weiss W, Salmhofer H, Schweigart U, Ilgmann K, Reichenberger J, Neu B and Classen M (2001) Reduced incidence of radiocontrast-induced nephropathy in ICU patients under theophylline prophylaxis: a prospective comparison to series of patients at similar risk. *Intensive Care Med* 27:1200-1209
12. McCullough PA, Stacul, F, Davidson, et al (2006) Overview. *Am J Cardiol* 98:2K-4K.
13. Bartholomew BA, Harjai KJ, Dukkupati S, Boura JA, Yerkey MW, Glazier S, Grines CL and O'Neill WW (2004) Impact of nephropathy after percutaneous coronary intervention and a method for risk stratification. *Am J Cardiol* 93:1515-1519
14. Weisbord SD, Mor MK, Resnick AL, Hartwig KC, Sonel AF, Fine MJ and Palevsky PM (2008) Prevention, incidence, and outcomes of contrast-induced acute kidney injury. *Arch Intern Med* 168:1325-1332
15. Bagshaw SM, Mortis G, Doig CJ, Godinez-Luna T, Fick GH and Laupland KB (2006) One-year mortality in critically ill patients by severity of kidney dysfunction: a population-based assessment. *Am J Kidney Dis* 48:402-409

16. Chew DP, Astley C, Molloy D, Vaile J, De Pasquale CG and Aylward P (2006) Morbidity, mortality and economic burden of renal impairment in cardiac intensive care. *Intern Med J* 36:185-192
17. McCullough PA (2008) Acute kidney injury with iodinated contrast. *Crit Care Med* 36[Suppl]:S204-S211
18. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG and Levin A (2007) Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 11:R31
19. Knaus WA, Draper EA, Wagner DP and Zimmerman JE (1985) APACHE II: a severity of disease classification system. *Crit Care Med* 13:818-829
20. Chertow GM, Burdick E, Honour M, Bonventre JV and Bates DW (2005) Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 16:3365-3370
21. Solomon RJ, Mehran R, Natarajan MK, Doucet S, Katholi RE, Staniloae CS, Sharma SK, Labinaz M, Gelormini JL and Barrett BJ (2009) Contrast-induced nephropathy and long-term adverse events: cause and effect? *Clin J Am Soc Nephrol* 4:1162-1169

Table 1. Differences between patients with and those without contrast-induced acute kidney injury (CIAKI)

	No CIAKI N = 119	CIAKI N = 24	<i>P</i>
Age (yrs)	61 [49-73]	63 [53-78]	0.33
Male sex	74 (62.2)	15 (62.5)	0.98
SAPS II score	40 [28-57]	57 [41-78]	0.001
Admission category			
medical	83 (69.8)	14 (58.3)	
scheduled surgery	11 (9.2)	1 (4.2)	0.22
unscheduled surgery	25 (21)	9 (37.5)	
Mc Cabe class			
1	65 (54.6)	9 (37.5)	
2	38 (31.9)	8 (33.3)	0.08
3	16 (13.5)	7 (29.2)	
Serum creatinine (µmol/L) before administration of ICM	87 [68-120]	90 [64-128]	0.91
Preventive measure	6 (5)	1(4.2)	1
Risk factors for renal dysfunction within 48 hrs before ICM administration			
diabetes mellitus	24 (20.2)	4 (16.7)	1
myeloma	0 (0)	1 (4.2)	0.17
nephrotoxic drugs	22 (18.5)	7 (29.2)	0.26
sepsis	48 (40.3)	16 (66.7)	0.02
hemodynamic failure	14 (11.8)	11 (45.8)	< 0.001
New risk factors for renal dysfunction within 48 hrs after ICM administration			
nephrotoxic drugs	19 (16)	7 (29.2)	0.14
sepsis	30 (25.2)	7 (29.2)	0.63
hemodynamic failure	18 (15.1)	11 (45.8)	0.001

Results are expressed as median [interquartile range] or as number (percent).

ICM, iodinated contrast media.

Table 2. Differences between patients with contrast-induced acute kidney injury who received and who did not receive renal replacement therapy (RRT)

	No RRT N = 17	RRT N = 7	<i>P</i>
SAPS II	58 [44-72]	50 [37-92]	0.97
Non-renal SOFA score before ICM administration	5 [4-6]	7 [5-9]	0.24
Serum creatinine (µmol/L) before ICM administration	90 [63-128]	83 [66-198]	0.80
Risk factors for renal dysfunction within 48 hrs before ICM administration	14 (82.3)	6 (85.7)	1
diabetes mellitus	3 (17.7)	1 (14.3)	1
myeloma	1 (5.9)	0 (0)	1
nephrotoxic drugs	5 (29.4)	2 (28.6)	1
sepsis	10 (58.9)	6 (85.7)	0.37
hemodynamic failure	7 (41.2)	4 (57.1)	0.76
New risk factors for renal dysfunction within 48 hrs after ICM administration	9 (52.9)	6(85.7)	0.19
nephrotoxic drugs	5 (29.4)	2 (28.6)	1
sepsis	4 (23.5)	3 (42.9)	0.63
hemodynamic failure	6 (35.3)	5 (71.4)	0.19
Preventive measure	0 (0)	1 (14.3)	0.3
ICU mortality	7 (41.2)	5 (71.4)	0.37

Results are expressed as median [interquartile range] or as number (percent).

ICM, iodinated contrast media.

Table 3. Independent risk factors for intensive care unit mortality

Variable	OR	95% CI	<i>P</i>
CIAKI	3.48	1.10-11.46	0.04
SAPS II	1.03	1.01-1.05	0.03
Non-renal SOFA score	1.38	1.12-1.71	0.003

Hosmer-Lemeshow chi square = 9.7, *p* = 0.20, c statistic = 0.80.

CIAKI, contrast-induced acute kidney injury.

# **Conclusions et perspectives**

Après de longues années marquées par l'hétérogénéité, la confusion et l'absence d'avancée réelle, la recherche sur l'AKI en réanimation semble prendre un tournant décisif comme en témoigne la volonté internationale de s'accorder tant sur les critères diagnostiques que sur la prise en charge thérapeutique globale.<sup>1,3</sup>

Les travaux présentés ici s'inscrivent dans cette mouvance et sont autant de pierres à la construction d'un édifice, loin d'être achevé cependant. Leur intérêt est double, à la fois épidémiologique et méthodologique.

Du point de vue épidémiologique, des réponses précises à des questions clé dans le domaine et les axes principaux de la recherche de demain se dégagent nettement.

L'AKI en réanimation s'affirme comme un facteur de risque indépendant de mortalité. Cela peut paraître évident mais les données de la littérature le démontrant sont très peu nombreuses.<sup>22-24</sup> Par l'utilisation d'une définition diagnostique consensuelle, la première étude de cette thèse le confirme et augmente le niveau de preuve. Il faut souligner malgré tout que la problématique de la définition persiste. En effet, la classification RIFLE n'est peut-être pas l'outil optimal en ce sens qu'elle peut entraîner un biais de classement de par le caractère peu fiable du critère diurèse et les approximations faites des valeurs basales de créatininémie et du débit de filtration glomérulaire. Par ailleurs, la valeur de cette classification est fortement limitée par la non démonstration jusqu'alors d'un quelconque impact pronostique favorable : on classe simplement les malades en fonction de leur degré de dysfonction rénale mais aucune traduction thérapeutique susceptible de réduire la mortalité n'est proposée. Il se pourrait même que son application systématique conduise à des retards diagnostiques préjudiciables. La confrontation des performances respectives des biomarqueurs sériques et urinaires, tels que la cystatine C et la neutrophile gelatinase-associated lipocalin, et de la classification RIFLE s'avère dès à présent hautement nécessaire.



La deuxième étude de cette thèse ne permet pas d'apporter d'éléments nouveaux favorables à l'EER, pilier actuel du traitement reposant sur des critères extrêmement flous et n'ayant jamais fait la preuve concrète de son efficacité, principalement en raison d'une initiation probablement trop tardive mais aussi du fait des complications proprement dites de la technique. Ce résultat souligne la nécessité urgente de standardisation des pratiques en termes de diagnostic, de délai d'instauration, de modalité et de dose d'épuration. La place définitive de l'EER en réanimation ne pourra être établie qu'à cette seule condition.

La troisième étude portant sur l'AKI induite par les produits de contraste iodés attire l'attention sur un problème fréquent et grave quelque peu négligé par les réanimateurs. Les patients les plus exposés y sont clairement identifiés et leur pronostic n'est à l'évidence pas amélioré par l'EER. En accord avec les avis d'experts récents,<sup>1,3</sup> le rapport bénéfice / risques chez ces patients doit donc être soigneusement pesé et une technique diagnostique alternative envisagée aussi souvent que possible. Des études prospectives, multicentriques sont indispensables à une meilleure appréhension de cette complication. Elles devront se focaliser sur l'effet des mesures préventives, sur l'importance de la nature et de la quantité du produit de contraste utilisé, ainsi que sur l'évaluation du rendement diagnostique et thérapeutique.

Du point de vue méthodologique, le recours à des techniques originales renforce la portée et la fiabilité des résultats.

L'approche de Fine et Gray tenant compte de la notion de risques compétitifs et l'intégration de variables dépendantes du temps rendent la modélisation plus proche de la réalité et l'interprétation statistique plus précise comparativement aux modèles classiques. Ce type de modèle, encore trop largement sous-utilisé, mérite davantage de considération à l'avenir. Notons qu'il peut s'appliquer non seulement à l'étude de la mortalité quand la sortie vivant est le risque compétitif mais également à l'étude d'autres événements tels que la survenue d'infections nosocomiales, la mortalité jouant alors le rôle de risque compétitif.<sup>74, 75</sup>

En l'absence d'essai randomisé, le score de propension est incontestablement la méthode de choix pour mesurer l'effet d'un traitement. Cette technique est elle aussi largement sous-utilisée alors que bon nombre de traitements ou de procédures sont appliqués en réanimation sans preuve scientifique solide et que l'évaluation de leur efficacité par un essai randomisé se heurte à des obstacles d'ordre pratique ou éthique.

Enfin, la régression logistique semble en théorie moins adaptée à l'analyse de la mortalité en réanimation (ou de la mortalité hospitalière) que les nouveaux modèles de survie. Toutefois, la question de la meilleure approche statistique n'est pas tranchée.

Pour conclure, insistons sur le fait que le modèle idéal n'existe pas et que le meilleur choix sera toujours celui qui permettra de répondre le plus justement à la question posée. A ce titre la collaboration entre cliniciens, épidémiologistes et statisticiens est dans tous les cas aussi enrichissante que primordiale.

# Références

1. Dennen P, Douglas IS, Anderson R: Acute kidney injury in the intensive care unit: an update and primer for the intensivist. *Crit Care Med* 38:261-275, 2010
2. Kellum JA, Levin N, Bouman C, Lameire N: Developing a consensus classification system for acute renal failure. *Curr Opin Crit Care* 8:509-514, 2002
3. Brochard L, Abroug F, Brenner M, Broccard AF, Danner RL, Ferrer M, Laghi F, Magder S, Papazian L, Pelosi P, Polderman KH: An Official ATS/ERS/ESICM/SCCM/SRLF Statement: Prevention and Management of Acute Renal Failure in the ICU Patient: an international consensus conference in intensive care medicine. *Am J Respir Crit Care Med* 181:1128-1155, 2010
4. 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* 8:R204-212, 2004
5. Fine J, Gray JR: A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 94:496-509, 1999
6. Haveman JW, Gansevoort RT, Bongaerts AH, Nijsten MW: Low incidence of nephropathy in surgical ICU patients receiving intravenous contrast: a retrospective analysis. *Intensive Care Med* 32:1199-1205, 2006
7. Polena S, Yang S, Alam R, Gricius J, Gupta JR, Badalova N, Chuang P, Gintautas J, Conetta R: Nephropathy in critically ill patients without preexisting renal disease. *Proc West Pharmacol Soc* 48:134-135, 2005
8. Chertow GM, Christiansen CL, Cleary PD, Munro C, Lazarus JM: Prognostic stratification in critically ill patients with acute renal failure requiring dialysis. *Arch Intern Med* 155:1505-1511, 1995
9. Cosentino F, Chaff C, Piedmonte M: Risk factors influencing survival in ICU acute renal failure. *Nephrol Dial Transplant* 9 Suppl 4:179-182, 1994
10. de Mendonca A, Vincent JL, Suter PM, Moreno R, Dearden NM, Antonelli M, Takala J, Sprung C, Cantraine F: Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. *Intensive Care Med* 26:915-921, 2000
11. Liano F, Junco E, Pascual J, Madero R, Verde E: The spectrum of acute renal failure in the intensive care unit compared with that seen in other settings. The Madrid Acute Renal Failure Study Group. *Kidney Int Suppl* 66:S16-24, 1998
12. Mehta RL, Pascual MT, Soroko S, Savage BR, Himmelfarb J, Ikizler TA, Paganini EP, Chertow GM: Spectrum of acute renal failure in the intensive care unit: the PICARD experience. *Kidney Int* 66:1613-1621, 2004
13. Neveu H, Kleinknecht D, Brivet F, Loirat P, Landais P: Prognostic factors in acute renal failure due to sepsis. Results of a prospective multicentre study. The French Study Group on Acute Renal Failure. *Nephrol Dial Transplant* 11:293-299, 1996
14. Schaefer JH, Jochimsen F, Keller F, Wegscheider K, Distler A: Outcome prediction of acute renal failure in medical intensive care. *Intensive Care Med* 17:19-24, 1991
15. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Ronco C: Acute renal failure in critically ill patients: a multinational, multicenter study. *Jama* 294:813-818, 2005
16. Metnitz PG, Krenn CG, Steltzer H, Lang T, Ploder J, Lenz K, Le Gall JR, Druml W: Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. *Crit Care Med* 30:2051-2058, 2002
17. Kellum JA, Angus DC: Patients are dying of acute renal failure. *Crit Care Med* 30:2156-2157, 2002

18. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A: Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 11:R31, 2007
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* 23:1569-1574, 2008
20. Joannidis M, Metnitz B, Bauer P, Schusterschitz N, Moreno R, Druml W, Metnitz PG: Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. *Intensive Care Med* 35:1692-1702, 2009
21. Lopes JA, Fernandes P, Jorge S, Goncalves S, Alvarez A, Costa e Silva Z, Franca C, Prata MM: Acute kidney injury in intensive care unit patients: a comparison between the RIFLE and the Acute Kidney Injury Network classifications. *Crit Care* 12:R110, 2008
22. Bagshaw SM, George C, Dinu I, Bellomo R: A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. *Nephrol Dial Transplant* 23:1203-1210, 2008
23. Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, Kellum JA: RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. *Crit Care* 10:R73, 2006
24. Ostermann M, Chang RW: Acute kidney injury in the intensive care unit according to RIFLE. *Crit Care Med* 35:1837-1843; quiz 1852, 2007
25. Maccariello E, Soares M, Valente C, Nogueira L, Valenca RV, Machado JE, Rocha E: RIFLE classification in patients with acute kidney injury in need of renal replacement therapy. *Intensive Care Med* 33:597-605, 2007
26. Wolkewitz M, Beyersmann J, Gastmeier P, Schumacher M: Modeling the effect of time-dependent exposure on intensive care unit mortality. *Intensive Care Med* 35:826-832, 2009
27. Resche-Rigon M, Azoulay E, Chevret S: Evaluating mortality in intensive care units: contribution of competing risks analyses. *Crit Care* 10:R5, 2006
28. Cox D: Regression models and life tables. *J Roy Stat Assoc B* 34:187-220, 1972
29. Pepe MS, Mori M: Kaplan-Meier, marginal or conditional probability curves in summarizing competing risks failure time data? *Stat Med* 12:737-751, 1993
30. Beyersmann J, Schumacher M: Time-dependent covariates in the proportional subdistribution hazards model for competing risks. *Biostatistics* 9:765-776, 2008
31. Wolkewitz M, Vonberg RP, Grundmann H, Beyersmann J, Gastmeier P, Barwolff S, Geffers C, Behnke M, Ruden H, Schumacher M: Risk factors for the development of nosocomial pneumonia and mortality on intensive care units: application of competing risks models. *Crit Care* 12:R44, 2008
32. 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* 24:192-198, 1996
33. Mehta RL, Pascual MT, Gruta CG, Zhuang S, Chertow GM: Refining predictive models in critically ill patients with acute renal failure. *J Am Soc Nephrol* 13:1350-1357, 2002
34. Joffe MM, Rosenbaum PR: Invited commentary: propensity scores. *Am J Epidemiol* 150:327-333, 1999
35. Rosenbaum PR, Rubin DB: The central role of the propensity score in observational studies for causal effects. *Biometrika* 70:41-55, 1983

36. Rosenbaum PR, Rubin DB: Reducing bias in observational studies using subclassification on the propensity score. *J Am Stat Assoc* 79:516-524, 1984
37. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T: Variable selection for propensity score models. *Am J Epidemiol* 163:1149-1156, 2006
38. Rubin DB, Thomas N: Matching using estimated propensity scores: relating theory to practice. *Biometrics* 52:249-264, 1996
39. Dalkey N, Helmer O: An experimental application of the Delphi method to the use of experts. *Management science* 9:458-467, 1963
40. Critcher C, Gladstone B: Utilizing the Delphi technique in policy discussion: a case study of a privatized utility in Britain. *Public administration* 76:434-449, 1998
41. McKenna H: The Delphi technique: a worthwhile research approach for nursing? *Journal of advanced nursing* 19:1221-1225, 1994
42. Weitzen S, Lapane KL, Toledano AY, Hume AL, Mor V: Principles for modeling propensity scores in medical research: a systematic literature review. *Pharmacoepidemiol Drug Saf* 13:841-853, 2004
43. Weitzen S, Lapane KL, Toledano AY, Hume AL, Mor V: Weaknesses of goodness-of-fit tests for evaluating propensity score models: the case of the omitted confounder. *Pharmacoepidemiol Drug Saf* 14:227-238, 2005
44. Seeger JD, Kurth T, Walker AM: Use of propensity score technique to account for exposure-related covariates: an example and lesson. *Med Care* 45:S143-148, 2007
45. D'Agostino RB, Jr.: Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 17:2265-2281, 1998
46. Austin PC: The performance of different propensity score methods for estimating marginal odds ratios. *Stat Med* 26:3078-3094, 2007
47. Cigarroa RG, Lange RA, Williams RH, Hillis LD: Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. *Am J Med* 86:649-652, 1989
48. Lautin EM, Freeman NJ, Schoenfeld AH, Bakal CW, Haramati N, Friedman AC, Lautin JL, Braha S, Kadish EG, Sprayregen S, et al.: Radiocontrast-associated renal dysfunction: incidence and risk factors. *AJR Am J Roentgenol* 157:49-58, 1991
49. Levy EM, Viscoli CM, Horwitz RI: The effect of acute renal failure on mortality. A cohort analysis. *Jama* 275:1489-1494, 1996
50. Parfrey PS, Griffiths SM, Barrett BJ, Paul MD, Genge M, Withers J, Farid N, McManamon PJ: Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. *N Engl J Med* 320:143-149, 1989
51. Weisberg LS, Kurnik PB, Kurnik BR: Risk of radiocontrast nephropathy in patients with and without diabetes mellitus. *Kidney Int* 45:259-265, 1994
52. Gruberg L, Mintz GS, Mehran R, Gangas G, Lansky AJ, Kent KM, Pichard AD, Satler LF, Leon MB: The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. *J Am Coll Cardiol* 36:1542-1548, 2000
53. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW: Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med* 103:368-375, 1997
54. Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, Singh M, Bell MR, Barsness GW, Mathew V, Garratt KN, Holmes DR, Jr.: Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 105:2259-2264, 2002

55. Marenzi G, Lauri G, Assanelli E, Campodonico J, De Metrio M, Marana I, Grazi M, Veglia F, Bartorelli AL: Contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 44:1780-1785, 2004
56. Sadeghi HM, Stone GW, Grines CL, Mehran R, Dixon SR, Lansky AJ, Fahy M, Cox DA, Garcia E, Tchong JE, Griffin JJ, Stuckey TD, Turco M, Carroll JD: Impact of renal insufficiency in patients undergoing primary angioplasty for acute myocardial infarction. *Circulation* 108:2769-2775, 2003
57. Solomon RJ, Mehran R, Natarajan MK, Doucet S, Katholi RE, Staniloae CS, Sharma SK, Labinaz M, Gelormini JL, Barrett BJ: Contrast-induced nephropathy and long-term adverse events: cause and effect? *Clin J Am Soc Nephrol* 4:1162-1169, 2009
58. McCullough PA, Stacul F, Davidson, et al: Overview. *Am J Cardiol* 98:2K-4K., 2006
59. Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ: Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med* 348:491-499, 2003
60. Barrett BJ, Carlisle EJ: Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. *Radiology* 188:171-178, 1993
61. Barrett BJ, Parfrey PS: Prevention of nephrotoxicity induced by radiocontrast agents. *N Engl J Med* 331:1449-1450, 1994
62. Chalmers N, Jackson RW: Comparison of iodixanol and iohexol in renal impairment. *Br J Radiol* 72:701-703, 1999
63. McCullough PA, Bertrand ME, Brinker JA, Stacul F: A meta-analysis of the renal safety of isosmolar iodixanol compared with low-osmolar contrast media. *J Am Coll Cardiol* 48:692-699, 2006
64. Merten GJ, Burgess WP, Gray LV, Holleman JH, Roush TS, Kowalchuk GJ, Bersin RM, Van Moore A, Simonton CA, 3rd, Rittase RA, Norton HJ, Kennedy TP: Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *Jama* 291:2328-2334, 2004
65. Mueller C, Buerkle G, Buettner HJ, Petersen J, Perruchoud AP, Eriksson U, Marsch S, Roskamm H: Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med* 162:329-336, 2002
66. Rudnick MR, Goldfarb S, Wexler L, Ludbrook PA, Murphy MJ, Halpern EF, Hill JA, Winniford M, Cohen MB, VanFossen DB: Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial. The Iohexol Cooperative Study. *Kidney Int* 47:254-261, 1995
67. Bartholomew BA, Harjai KJ, Dukkipati S, Boura JA, Yerkey MW, Glazier S, Grines CL, O'Neill WW: Impact of nephropathy after percutaneous coronary intervention and a method for risk stratification. *Am J Cardiol* 93:1515-1519, 2004
68. Weisbord SD, Mor MK, Resnick AL, Hartwig KC, Sonel AF, Fine MJ, Palevsky PM: Prevention, incidence, and outcomes of contrast-induced acute kidney injury. *Arch Intern Med* 168:1325-1332, 2008
69. Schoenfeld D: Survival methods, including those using competing risk analysis, are not appropriate for intensive care unit outcome studies. *Crit Care* 10:103, 2006
70. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, Takagaki TY, Carvalho CR: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 338:347-354, 1998
71. Chevret S: Logistic or Cox model to identify risk factors of nosocomial infection: still a controversial issue. *Intensive Care Med* 27:1559-1560, 2001

72. Hauck WW: A comparison of the logistic risk function and the proportional hazards model in prospective epidemiologic studies. *J Chronic Dis* 38:125-126, 1985
73. Ingram DD, Kleinman JC: Empirical comparisons of proportional hazards and logistic regression models. *Stat Med* 8:525-538, 1989
74. Alberti C, Brun-Buisson C, Chevret S, Antonelli M, Goodman SV, Martin C, Moreno R, Ochagavia AR, Palazzo M, Werdan K, Le Gall JR: Systemic inflammatory response and progression to severe sepsis in critically ill infected patients. *Am J Respir Crit Care Med* 171:461-468, 2005
75. Alberti C, Metivier F, Landais P, Thervet E, Legendre C, Chevret S: Improving estimates of event incidence over time in populations exposed to other events: application to three large databases. *J Clin Epidemiol* 56:536-545, 2003