Author's response to reviews

Title: Epidemiology of acute kidney injury in Hungarian intensive care units: a multicenter, prospective, observational study

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Version: 3 Date: 14 April 2011

Author's response to reviews: see over
Author's response to reviews

Title: Epidemiology of acute kidney injury in Hungarian intensive care units: a multicenter, prospective, observational study.

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Version: 2 Date: 14 March 2011

Author's response to reviews: see over
Reviewer's report

Title: Epidemiology of acute kidney injury in Hungarian intensive care units: a multicenter, prospective, observational study

Version: 1 Date: 29 October 2010

Reviewer: Marlies Ostermann

Reviewer's report:

Major compulsory revisions:

1. The authors used the AKIN classification to define AKI. Transplant patients and patients on dialysis were excluded. How did they deal with patients with pre-existing chronic kidney disease? Does the study include any patients with AKI on the background of chronic kidney disease?

12 patients had pre-existing chronic kidney disease. In these cases development of AKI was considered as acute on chronic renal failure and these patients were included into the study. (Page 3)

Chronic kidney disease patients on dialysis (n=3) and theoretically the renal transplant patients (n=0) were excluded from the analysis. 12 patients had creatinine level >300 µmol/L on admission. In these cases development of AKI was considered as acute on chronic renal failure.

2. Did the authors assess trends in serum creatinine in both directions, ie. How did they deal with patients with a raised serum creatinine on admission to ICU which subsequently fell?

We considered only the raising creatinine levels (Page 3)

Serum creatinine on ICU admission was used as a reference value, staging was based on the appropriate increase within the 48 hour observation. Declines in serum creatinine were not coded as AKI.

3. What was the timing of AKI? Was there a difference between AKI within the first 48 hours of ICU admission versus AKI which developed later?

We didn’t distinguish early and late AKI, it was one of the limitations of the study. (Page 8)

Finally, we didn’t distinguish early and late AKI.

4. Figure 1: the authors state that 39% of AKI was related to hypovolaemia. Strictly speaking, these patients do not fulfill the criteria of the AKIN classification. According to the AKIN criteria, AKI can only be diagnosed “after obstruction or other easily reversible causes of
reduced urine output have been excluded”. The authors should comment on whether this criterion of the AKIN classification was fulfilled.

The diagnosis of hypovolemia was based mainly on basic hemodynamic data and clinical impressions. See detailed discussion on Page 7.

Since our study protocol did not require an invasive hemodynamic monitoring, we could not assess exactly the volume-status of patients on ICU-admission. We evaluated it as a major limitation of our study because the diagnosis of hypovolemia was based mainly on basic hemodynamic data and clinical impressions.

5. Page 6, last sentence: What is the evidence for the statement “The higher mortality of AKI in Hungarian ICUs can be explained by factors, such as higher incidence of malignancy and non-uniform treatment principles”?

We compared our results to the cohort analysis of Joannidis et al and found more than double malignancy occurrence, and we may suppose that lack of the widely accepted protocols can contribute to the higher mortality (Page 7-8).

The higher mortality of AKI in Hungarian ICUs can be explained also by factors, such as higher incidence of malignancy and non-uniform treatment principles. In the cohort analysis of Joannidis et al [26] 6.1 % of AKI was related to non-metastatic cancer patients, while in our study it was 13%. The other reason may be that in Hungary there are not uniform protocols for treatment of AKI (different: the timing of RRT, the treatment modalities and doses of RRT, continuous vs. intermittent diuretic therapy).

6. Page 7: The discussion includes data on dose of renal replacement therapy. It would be more appropriate to include this information in the Results section.

We moved the data on dose of RRT to the Result section (Page 5).

7. The discussion should include a paragraph on limitations of the study.

We included the limitations of our study into the Discussion (Page 8).

The limitations of our study: Hypovolemia was not exclusion criteria in classification by AKIN. We applied early goal directed volume resuscitation, while followed the urine output hourly. If during the first six hours period the urine output raised above 0.5 ml/kg/h we didn’t classified the patient for AKI 1 stage. Secondly, the Hungarian ICU-s hasn’t uniform protocol for treatment of AKI, so we couldn’t compare the different ICU-s. Finally, we didn’t distinguish early and late AKI.
8. Tables: The tables should include percentages, either instead or in addition to the actual number of patients. In addition, I am not sure how useful it is to distinguish between male and female patients in all categories.

We deleted male and female distinguishing from Table 1 and mentioned it in the text (Page 4).

Because there were no significant differences among the examined variables in respect of the gender, in the following analyses the data were drawn together.

Minor essential revision:

1. Page 6, 4th line: I would suggest to say "AKI has long been recognised as a complication after surgery" instead of "surgical complication".

We have done the suggestion to your minor revision (Page 6).

AKI has long been recognized as a devastating complication after surgery [3, 29] and postoperative AKI remains a leading cause of morbidity, mortality and prolonged hospital stay [18, 21, 29-32].

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not statistician.

Declaration of competing interests:
I declare that I have no competing interests.
Reviewer's report

Title: Epidemiology of acute kidney injury in Hungarian intensive care units: a multicenter, prospective, observational study

Version: 1 Date: 5 March 2011

Reviewer: Monique M Elseviers

Reviewer's report:
Epidemiology of acute kidney injury in Hungarian intensive care units: a multicenter, prospective, observational study

Laszlo Medve, Csaba Antek, Balazs Paloczi, Szilvia Kocsi, Bela Gartner, Zsuzsanna Marjanek, Gabor Bencsik, Peter Kanizsai and Tibor Gondos

Dear authors,

I read with interest your manuscripts describing the epidemiology of AKI in Hungarian ICUs. Your intention to investigate for the first time the epidemiology of AKI in Hungarian ICUs forms an attractive topic, particularly at the national level. The methodology used for data collection with the participation of different kind of hospitals and with an electronic data collection system enabling immediate control of the data looked promising. It is particularly in the handling of the data that important shortcomings could be noticed. Extra statistical advise is highly recommended.

1. Major Compulsory Revisions

1.1 Background – 2nd par:
Your second aim is to evaluate the impact of AKI on outcomes in the context of other risk factors – for this evaluation a much more systematic and in-depth comparison between risk factors and outcome in both groups (AKI versus non-AKI) needs to be performed completed with multivariate analysis to investigate the contribution of these risk factors on outcome

We accepted your advice and perform logistic regression analyses to investigate the contribution of the risk factors on the development of AKI and the outcome (Page 4, 5, 7-8, Table 3 and 5).

A forward stepwise logistic regression analysis (conditional) was perform to determine the independent risk factors for AKI and mortality The included variables were: age, gender, vasopressor requirement, AKI stages, SOFA, SAPS II, creatinine level at ICU admission and the maximum level during ICU staying, surgical/medical admission, the different diseases, sepsis, mechanical ventilation, as appropriate.

A logistic regression analysis was performed to analyse the predisposing factors for the incidence of AKI. Among the analysed parameters vasopressor treatment, SAPS II score, serum creatinine on ICU admission and sepsis were the independent risk factors for development of any stage
of AKI (Table 3). The same distribution was found when the independent predisposing factors for AKI Stage 3 were evaluated.

According to the logistic regression analysis (Table 5) age, mechanical ventilation, SOFA score and AKI Stage 3 were found as independent risk factors for ICU mortality. In respect of the hospital mortality only the higher age, the need of vasopressor treatment and the neurological diseases were the independent risk factors for the mortality.

In our study, sepsis was also the leading etiologic factor (in 44% of patients) of AKI, and was a highly significant independent risk factor for AKI.

In our study the age, the sepsis related variables (vasopressor treatment, mechanical ventilation, SOFA score) and the AKI Stage 3 were the highly significant risk factors for the ICU and the hospital mortality.

1.2 Methods - Statistical analysis
This section is incomplete and gives incorrect information
Incomplete: only continuous data can be expressed as mean or median – others are preferentially expressed as percentage – when and why you used median instead of mean?
Incorrect: median values are not analyzed with chi-square test

We corrected the mistake in respect of the chi-square test (Page 4). We used the median values instead of the means in cases when the distribution of data was asymmetric, not normal.

The mean values of the different groups were compared using two-sided t-test, the median values by the Kolmogorov-Smirnov test and the occurrence rates by the chi-square test.

1.3 Results
The order of presenting the results is confusing and not logic. The presentation of the results is incomplete, a large part of data analysis is lacking. Particularly the presentation of data in the tables shows important shortcomings: Table 1 and 2: why all results are separately presented by gender? Is this the most important discriminating factor? All tables: to see any difference between groups, it is highly recommended to express your categorical variables as percentage, not only as raw numbers P-values of .0000 do not exist in reality and are preferentially expressed as p<.001. Other p-values seem to be incorrect and needs to be carefully recalculated!

We tried to make a more complete presentation of the results (Page 5,6). We expressed the categorical variables as percentage too, and deleted the gender discrimination from the tables. We expressed p=0.0000 as p<0.001. We have done the recalculation of the other p values and found them they were correct.

Because there were no significant differences among the examined variables in respect of the gender, in the following analyses the data were drawn together. AKI patients tended to be older (64.9 vs. 57.6 years, p<0.001) and usually had more severe underlying diseases (SAPS II. 47.5
vs. 22, p<0.001, SOFA 6 vs. 2, p<0.001). The proportion of patients who needed mechanical ventilation during their ICU stay differed significantly in patients without or with AKI (33.4% and 75.0%, p<0.001) A similar difference was also observed in the vasopressor needs (12.1% vs. 51.8% in patients without and with AKI, respectively, p=0.0018).

One-hundred-twelve patients (24.4%) had AKI during their ICU stay. By AKIN criteria 53 patients (11.5%) were in Stage 1, 25 patients (5.5%) in Stage 2 and 34 patients (7.4 %) in Stage 3. Seventeen patients (15.2% of the AKI cases) had received renal replacement therapy.

The major reason for ICU admission was surgical in 64.3% (gastrointestinal tract surgery was the most common), followed by neurological, cardiovascular, pulmonary diseases and trauma cases (Table 2).

In 44.0% of patients, AKI was associated with septic shock (Figure 1). Sixteen percent of AKI was associated with major surgery, 20% was related to cardiogenic shock, 39% was related to hypovolemia, and 2% of AKI was potentially drug-related.

A logistic regression analysis was performed to analyse the predisposing factors for the incidence of AKI. Among the analysed parameters vasopressor treatment, SAPS II score, serum creatinine on ICU admission and sepsis were the independent risk factors for development of any stages of AKI (Table 3). The same distribution was found when the independent predisposing factors for AKI Stage 3 were evaluated.

1.4 Discussion
Limitations of your work are not handled
Several statements are not supported by the data.
Some examples:
- 1st par: ‘increased incidence of AKI’ compared to what?
- 2nd par: is drug toxicity the most important factor in the elderly?
- 8th par – last sentence: did you notice non-uniform treatment principles – this was not handled in the results

We included the limitations of our study into the Discussion (Page 8). We tried to explain more clearly our statements (Page 7-8).

The limitations of our study: Hypovolemia was not exclusion criteria in classification by AKIN. We applied early goal directed volume resuscitation, while followed the urine output hourly. If during the first six hours period the urine output raised above 0.5 ml/kg/h we didn’t classified the patient for AKI 1 stage. Secondly, the Hungarian ICU-s hasn’t uniform protocol for treatment of AKI, so we couldn’t compare the different ICU-s. Finally, we didn’t distinguish early and late AKI.

1.5 Conclusion
The conclusion is too vague. Not all aims of the study are handled.
We corrected our conclusion (Page 9).

The independent risk factors for the development of any stage of AKI were SAPS II score, serum creatinine on ICU admission, sepsis and vasopressor treatment. Age, sepsis related variables (vasopressor treatment, mechanical ventilation, SOFA score) and AKI Stage 3 were the highly significant risk factors for the ICU and the hospital mortality.

2. Minor Essential Revisions
• figure 1: correct ‘DRUG-related’
• abstract: total sample size is lacking in results section
• reference 3: year of publication is not correct

We corrected your suggestions as minor essential revisions.

3. Discretionary Revisions
• abstract method: confusing presentation of the period of data collection for a European readership
• ref 5 and 6: outdated references on incidence of AKI

We corrected the date format in the Abstract (Page 1) and removed Ref. 5 and 6 from the manuscript.

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests.
Reviewer's report

Title: Epidemiology of acute kidney injury in Hungarian intensive care units: a multicenter, prospective, observational study

Version: 1 Date: 7 March 2011

Reviewer: Zaccaria Ricci

Reviewer's report:

Medve and coworkers conducted a 60 days epidemiologic study on AKI in 7 Hungarian ICUs. The authors utilized AKIN criteria to diagnose AKI. The methodology of this epidemiological study is interesting because it was conducted (as far as they claim) for the first time in Hungary and because the authors utilized AKIN criteria for their research: their results are finally directly comparable to those of other centers/nations.

The major concern of this study is that, from the epidemiological stand point, their sample size (and observational time) is relatively small. Furthermore, the derived information may be of some interest for Hungarian healthcare, since it looks like the data reported from the authors substantially confirm a good quality of care, in line with currently reported in multinational observations (as also punctually discussed by the authors). Nevertheless, they do not add significant insights to the readers. In my opinion a good point to make the article original, might be to identify some critical points of Hungarian AKI treatment strategy and to directly compare them to some other “reference” AKIN data (i.e. Joannidis M, et al Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. Intensive Care Med. 2009 Oct;35(10):1692-702) analyzing and discussing where they do better and where they do worse, eventually explaining why.

We included and discussed a little bit more the results of Joannidis et al in the discussion (Page 6-7).

Joannidis M and co-workers analysed by AKIN criteria the SAPS 3 database, found the incidence 28.5 %, that is very similar to our data (24.4%) [26]. While, they didn’t found the difference between AKI 1 and 2, in our study AKI 1 (11.5%) was double to AKI 2 (5.5%). The difference may arise from the fact, that they assessing urine-output only at 24-hours intervals and could not distinguish between the AKIN stage 1 and 2. We found that the incidence of 7.4% in AKI 3 is better comparable to the data of Osterman [14] and Thakar [19], than the incidence of 13.8% of a cohort analysis [26].

We could demonstrate that the incidence rate of AKI is highest in elderly patients, who make up an ever-growing segment of the population. In the aging population, there is heightened susceptibility to drug toxicity, partially owing to altered drug pharmacokinetics and pharmacodynamics. Furthermore, elderly people consume twice as many medications overall, including nephrotoxic agents, than younger patients [16, 27]. In our study, AKI patients were significantly older with a higher SAPS II score which was found as an independent risk factor for AKI.
Vasopressor treatment was a risk factor for the development of any stages of AKI, while mechanical ventilation was an independent risk factor for ICU mortality.

The higher mortality of AKI in Hungarian ICUs can be explained also by factors, such as higher incidence of malignancy and non-uniform treatment principles. In the cohort analysis of Joannidis et al [26] 6.1% of AKI was related to non-metastatic cancer patients, while in our study it was 13%. The other reason may be that in Hungary there are not uniform protocols for treatment of AKI (different: the timing of RRT, the treatment modalities and doses of RRT, continuous vs. intermittent diuretic therapy). In our study the age, the sepsis related variables (vasopressor treatment, mechanical ventilation, SOFA score) and the AKI Stage 3 were the highly significant risk factors for the ICU and the hospital mortality.

We presented the mortality data in more details together with the p values (Page 5) in the Results.

The overall in-hospital mortality rate of AKI was 49% (55/112). The ICU mortality rate was 39.3% (44/112) (Table 4). Any degree of AKI was associated with a significantly increased all-cause ICU (9.5% vs. 29.3%, p<0.001) and hospital mortality (16.1% vs. 39.3%, p<0.001) compared with not having AKI. For patients admitted with AKI to the ICU, the median length of stay at the ICU increased by 120% (2 vs. 4.5 day, p<0.0001) and the median length of hospitalization by 35% (10 vs. 13.5 day, p=0.005), compared to patient without AKI.

We have performed the suggested logistic regression analyses to investigate the contribution of the risk factors on the development of AKI and the mortality (Page 4, 5, 7-8, Table 3 and 5).

A forward stepwise logistic regression analysis (conditional) was perform to determine the independent risk factors for AKI and mortality. The included variables were: age, gender, vasopressor requirement, AKI stages, SOFA, SAPS II, creatinine level at ICU admission and the maximum level during ICU staying, surgical/medical admission, the different diseases, sepsis, mechanical ventilation, as appropriate.

A logistic regression analysis was performed to analyse the predisposing factors for the incidence of AKI. Among the analysed parameters vasopressor treatment, SAPS II score, serum creatinine on ICU admission and sepsis were the independent risk factors for development of any stage of AKI (Table 3). The same distribution was found when the independent predisposing factors for AKI Stage 3 were evaluated.

According to the logistic regression analysis (Table 5) age, mechanical ventilation, SOFA score and AKI Stage 3 were found as independent risk factors for ICU mortality. In respect of the hospital mortality only the higher age, the need of vasopressor treatment and the neurological diseases were the independent risk factors for the mortality.
In our study, sepsis was also the leading etiologic factor (in 44% of patients) of AKI, and was a highly significant independent risk factor for AKI.

In our study the age, the sepsis related variables (vasopressor treatment, mechanical ventilation, SOFA score) and the AKI Stage 3 were the highly significant risk factors for the ICU and the hospital mortality.

Minor

The authors must present the mortality data for AKI and non AKI patients: as is this section lacks clarity. The authors should report p values of their main findings in the results section text.

The authors state that “Any degree of AKI was associated with a significantly increased all-cause ICU and hospital mortality compared with not having AKI” but in table 4 the in-hospital mortality difference between AKI and non AKI patients appeared non significant: please specify better. As far as I understand, the patients with AKI that survived ICU are 112-44= 68; of these 11 died after the ICU. On the other side 347 without AKI had an ICU mortality of 77 patients: these 270 survivors had an in-hospital mortality of 34 pts: all these informations must be specified with related “%’s and “p”s!

I understand the the sample size is relatively small, but it would add much interest to know (or actually, to have the confirmation that) AKI is an independent risk for mortality in a multivariate analysis (the authors did collect a lot of data not to do this kind of analysis!).

We have clarified all in the result and discussion sections and changed as indicated by the reviewer.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests
Reviewer's report

Title: Epidemiology of acute kidney injury in Hungarian intensive care units: a multicenter, prospective, observational study

Version: 1 Date: 8 March 2011

Reviewer: Emmanuel Burdmann

Medve et al assessed prospectively the rate of AKI by AKIN definition in seven Hungarian ICUs. The manuscript reads well and the results, although confirmatory, are interesting.

Points about the manuscript:

Positives

The strength of the current report it is it prospective nature and the use of AKIN classification. Most of the manuscripts widely cited about AKI in the ICU are retrospective analysis and few used AKIN definition.

Major compulsory revisions:

1. How were selected the ICUs? How many ICUs exist in Hungarian? How the authors can be sure that the numbers of ICUs and patients analyzed are really representative for the country?

In Hungary we have ~70 interdisciplinary ICUs, and we chose 1/10th of them from different levels. (Page 2)

The participant centres represent the spectrum of Hungarian ICUs (each of them were multidisciplinary non-cardiac ICU, representing the occurrence ratio of ICU patients in Hungary):

2. How was selected the time frame of two months? Might this time limit introduce a bias for seasonality of diseases?

According to our knowledge there is no seasonal difference in the incidence of AKI. The study time frame was selected arbitrarily.

3. There are missing patients? We can only speak about incidence if all patients admitted to the ICUS during the study were included in the analysis. Please, clarify.

Only 3 newly admitted patients were excluded from the study due to end-stage kidney diseases (Page 3).

Chronic kidney disease patients on dialysis (n=3) and theoretically the renal transplant patients (n=0) were excluded from the analysis.

4. It is not clear if the patients developed AKI in the ICU or if some of them were already admitted in the ICU with AKI. If that was the case, how was defined the baseline serum creatinine? Please, clarify both questions.
We had no previously proven AKI cases, only 48 hours after the ICU admission. To diagnose AKI we need the changes, not only the baseline values. The baseline value was the first creatinine level in the ICU.

5. How many patients were categorized as AKI using the creatinine versus the urine output criteria? When a patient was defined as AKI by one but not by the other parameter, how the authors proceeded?

According to the definition of AKIN we can diagnose AKI using serum creatinine and/or urine output changes. We did not distinguish the two inclusion criterions.

6. Which method was used for creatinine analysis? They were done in a core laboratory or each hospital performed its own? If that is the case, did the authors test for inter-variability among the laboratories?

Measurements of serum creatinine levels were done in its own laboratory of each hospital. In Hungary to get an international accreditation of the laboratories is obligatory to each hospital using internationally accepted reference samples.

7. The way the results were written is a little confuse. I suggest describing the entire sample first followed by the AKI patients, comparing them with the whole population.

We tried to accept your suggestions (Page 4-5).

Altogether 459 patients (aged 59.6±16.2 years, male/female ratio 258/201) were entered into the study. Baseline characteristics of the patients are summarized in Table 1. Because there were no significant differences among the examined variables in respect of the gender, in the following analyses the data were drawn together. AKI patients tended to be older (64.9 vs. 57.6 years, p<0.001) and usually had more severe underlying diseases (SAPS II 47.5 vs. 22, p<0.001, SOFA 6 vs. 2, p<0.001). The proportion of patients who needed mechanical ventilation during their ICU stay differed significantly in patients without or with AKI (33.4% and 75.0%, p<0.001) A similar difference was also observed in the vasopressor needs (12.1% vs. 51.8% in patients without and with AKI, respectively, p=0.0018).

One-hundred-twelve patients (24.4%) had AKI during their ICU stay. By AKIN criteria 53 patients (11.5%) were in Stage 1, 25 patients (5.5%) in Stage 2 and 34 patients (7.4 %) in Stage 3. Seventeen patients (15.2% of the AKI cases) had received renal replacement therapy.

The major reason for ICU admission was surgical in 64.3% (gastrointestinal tract surgery was the most common), followed by neurological, cardiovascular, pulmonary diseases and trauma cases (Table 2).

In 44.0% of patients, AKI was associated with septic shock (Figure 1). Sixteen percent of AKI was associated with major surgery, 20% was
related to cardiogenic shock, 39% was related to hypovolemia, and 2% of AKI was potentially drug-related.

A logistic regression analysis was performed to analyse the predisposing factors for the incidence of AKI. Among the analysed parameters vasopressor treatment, SAPS II score, serum creatinine on ICU admission and sepsis were the independent risk factors for development of any stages of AKI (Table 3). The same distribution was found when the independent predisposing factors for AKI Stage 3 were evaluated.

Renal replacement therapy

Among AKI Stage 3 patients 50% (17/34) received renal replacement therapy. The overall utilization of intermittent renal replacement therapy (IRRT) was high, with 64.8% (among all patients with RRT). All patients were treated with a veno-venous technique. The most common mode in the IRRT group was IHD (88%) and in the CRRT group CVVHDF (94%). The median filtration dose was a regimen of 20 mL/kg/h.

Mortality and lengths of stay

The overall in-hospital mortality rate of AKI was 49% (55/112). The ICU mortality rate was 39.3% (44/112) (Table 4). Any degree of AKI was associated with a significantly increased all-cause ICU (9.5% vs. 29.3%, p<0.001) and hospital mortality (16.1% vs. 39.3%, p<0.001) compared with not having AKI. For patients admitted with AKI to the ICU, the median length of stay at the ICU increased by 120% (2 vs. 4.5 day, p<0.0001) and the median length of hospitalization by 35% (10 vs. 13.5 day, p=0.005), compared to patient without AKI. According to the logistic regression analysis (Table 5) age, mechanical ventilation, SOFA score and AKI Stage 3 were found as independent risk factors for ICU mortality. In respect of the hospital mortality only the higher age, the need of vasopressor treatment and the neurological diseases were the independent risk factors for the mortality.

8. The authors must include the potential limitations for the study results in the manuscript.

We included the limitations of our study into the Discussion (Page 8).

The limitations of our study: Hypovolemia was not exclusion criteria in classification by AKIN. We applied early goal directed volume resuscitation, while followed the urine output hourly. If during the first six hours period the urine output raised above 0.5 ml/kg/h we didn’t classified the patient for AKI 1 stage. Secondly, the Hungarian ICU-s hasn’t uniform protocol for treatment of AKI, so we couldn’t compare the different ICU-s. Finally, we didn’t distinguish early and late AKI.
Minor essential revisions:

1. Minor observation: in the figure there are two misspellings: hypovolemie and drud-related.

We corrected the misspellings in Figure 1.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.