

Editorial

Big data in nephrology—a time to rethink

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Big data are abundant in nephrology. We celebrate big data; we embrace them because of their sample sizes and give them space in the most respected journals. We make policy and funding decisions based on big data. But what happened to the interventional studies? Could the ready presence of big data be a bane of nephrology? What if the interpretations of the big data are flawed? Few of us really understand the statistical methods that underlie these big data, so all we read is the conclusion. We will take the example of a study published in this issue of *NDT* to note that the interpretation of big data by another set of nephrologists could lead to a conclusion quite contrary to that of the authors.

To publish a paper using big data, we need three things: big data, an outcome and a statistical method. The article by Chou *et al.* [1] has all three ingredients. What if each of these three ingredients is messy—as is often the case—can we still rely on the conclusions? We will point out how we might reach a very different conclusion using the same data presented. We will question three factors: flaws in the data, selection of the outcome and the statistical methods. Thus, could that lead to a different conclusion? We do so not to criticize the study of Chou *et al.* [1] as much as to illustrate that we should not blindly trust big data. We use this as an opportunity to call for interventional studies that are sorely lacking in nephrology.

BIG DATA

The study of Chou *et al.* [1] asks the question whether change in blood pressure (BP) during dialysis for end-stage renal disease and “intradialytic hypotension” is related to mortality. This study is certainly big. The authors started with 208 820 incident dialysis patients but ended with 112 013 in the cohort. The 46% drop-out rate was in large part due to >46 000 patients not being dialyzed in the participating hemodialysis (HD) units for ≥ 60 days. Thus, despite the large sample size, the generalizability is reduced because these results would not apply to those who did not survive the first 2 months—the time at which the mortality risk is the greatest.

Big data typically rely on analyzing electronic databases of routinely gathered clinical information. The quality of these data may not be the ideal. For instance, this study analyzed peridialytic BP. However, other measures of BP in HD patients have been shown to be a superior correlate of mortality. For example, recent analyses of the prospective Chronic Renal Insufficiency Cohort found that while peridialytic BP has a U-shaped relationship with all-cause mortality and cardiovascular events, BP measured outside of the HD unit has a linear relationship with both all-cause mortality [2] and cardiovascular events [3], similar to the experience in other hypertensive populations. Other reports have shown home BP measures to be superior to peridialytic BP for correlation to end-organ damage [4], as well as for predicting cardiovascular events and all-cause mortality [5].

Additionally, big data cannot analyze that which is not easily gleaned from electronic databases. In this case there is no information available on antihypertensive drug usage or prescribed changes in dry weight that may illuminate whether the observed low BP values were the result of medical interventions or the consequence of worsening underlying illness. This distinction is important because the answer impacts whether and how aggressive dialysis practitioners should be in treating hypertensive HD patients. Although low BP associates with mortality, meta-analyses of the available randomized clinical trials of antihypertensive medications in HD have not shown harm and instead showed benefit in the form of reduced cardiovascular events, with the effect most pronounced in the cohort of patients with known hypertension at baseline [6].

OUTCOME DEFINITION

Was the outcome of all-cause mortality chosen by the authors appropriate? Dialysis patients do not rate all-cause mortality as a high priority, rather fatigue, energy, ability to travel and quality of life are more important for them. For HD nurses and technicians, sudden syncopal episodes and machine alarms may be more important. Furthermore, if a potential causal link between

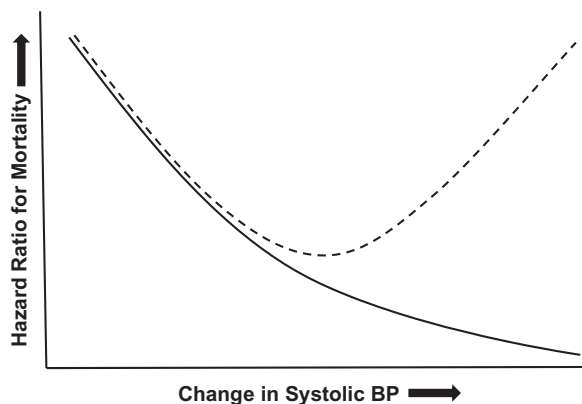


FIGURE 1: In an unadjusted analysis, a greater change in SBP on dialysis is associated with a decreasing hazard ratio for all-cause mortality, as illustrated by the solid line. After extensive statistical adjustment, the relationship is altered such that a large change in SBP is associated with a high hazard ratio, as represented by the dashed line.

hypotension and poor outcomes is sought, then the most specific hard outcome to measure would be cardiovascular events or cardiovascular mortality, not all-cause mortality. While all-cause mortality can be reliably ascertained in a retrospective fashion on a large scale, reliable identification of cardiovascular events requires a prospective study by investigators experienced with adjudicating such events.

METHODOLOGY

Was the methodology appropriate? The definition of intradialytic hypotension was not standard in this study. The European Best Practices Guidelines for HD define intradialytic hypotension as a drop in BP that is both associated with symptoms and that requires an acute nursing intervention [7]. This definition focuses on the individual HD session whereas the definitions for intradialytic hypotension in the report by Chou *et al.* [1] used BP values averaged over >3 months and does not use the standard definition.

Chou *et al.* [1] report that frequent declines in systolic BP (SBP) associate with mortality. However, this may not be cause and effect. Hypotension may simply be a marker of severity of underlying illness that itself is the cause of subsequent mortality. This relationship is likely to be most pronounced in a cohort of more acutely ill patients. Indeed, lower BP has been shown to be associated with increased mortality for incident peritoneal dialysis (PD) patients, whereas in the same cohort lower BP was protective for those patients with a dialysis vintage of at least 6 years [8]. Most importantly, when only the incident PD patients healthy enough to be listed for transplant were analyzed, lower BP was still protective. In fact, the Chou *et al.* [1] study includes findings that support the notion that comorbidity and severity of illness are likely major contributors to the hypotension associated with mortality. For example, the average nadir SBP < 90 mmHg over the incident 3 months of HD was associated with a clinically major hazard ratio >4 without any adjustment, but after full adjustment, including for comorbidities and

markers of inflammation, the hazard ratio for all-cause mortality at 1 year was down to 1.5. It is certainly possible that if more granular data were available to allow adjustment for severity and not just the presence of comorbidities, such as heart failure class in the 36% of the cohort reported to have a history of congestive heart failure, then the hazard ratios may have been even further mitigated. It should be noted that whereas a hazard ratio of 4 may be relevant for individual-level decision making, a hazard ratio of 1.5 is of epidemiological interest only [1].

Most important is the question of statistical adjustment. In a randomized trial, both known and unknown confounders can be balanced by randomization, but retrospective studies require statistical adjustment to account for known confounders. The study by Chou *et al.* [1] adjusted for both the predialysis SBP and predialysis diastolic BP (DBP) simultaneously. In such a model predicting all-cause mortality, a higher SBP and lower DBP relates to mortality [9]. This is because the two considered together assess arterial stiffness. What does it mean when one adjusts a decline in SBP during dialysis for arterial stiffness? Could there be an interaction between arterial stiffness and a decrease in SBP with respect to all-cause mortality? In other words, is it possible that those with the greatest declines in SBP have an increased mortality only when they have stiff arteries? Or could the arterial stiffness be in the causal pathway that relates a decline in SBP during dialysis to all-cause mortality? This last question is not simply of academic interest. This is because statistical adjustment for a factor that lies on the causal pathway between an exposure and an outcome can fundamentally alter that relationship between the risk factor and the outcome.

Expounding further on this point of adjustment, the data were adjusted for ultrafiltration volume and dialysis time, so effectively, ultrafiltration rate. Is it possible that those who have the greatest SBP decline with the least ultrafiltration rate have worse outcomes? These data are not presented, so we cannot address these questions, but it is clear that the adjustments fundamentally change the outcomes. Note in Figure 3B from the report by Chou *et al.* [1] in an unadjusted analysis, those with the smallest decrease in SBP have an increased mortality. Their Figure 3B, redrawn conceptually as Figure 1, shows that the lowest sextile had the highest unadjusted mortality. In other words, if SBP does not decline with dialysis, all-cause mortality is elevated. The greatest declines in SBP (>50 mmHg systolic) had the lowest hazards for mortality. One may therefore reasonably conclude that a decrease in SBP is physiologic and associated with longer life in a dialysis patient (Figure 1, solid line). However, when one adjusts for the ultrafiltration volume, SBP, DBP and dialysis duration, the data are interpreted quite differently (Figure 1, broken line).

Finally, there is a pearl potentially hidden in the article—not hypotension, but intradialytic hypertension. Figure 3A from the paper by Chou *et al.* [1] shows a strong association between intradialytic hypertension and 5-year mortality, even after full adjustment. In fact, only 6% of the cohort had the largest decrease in SBP (> 50 mmHg), while even more patients had the smallest decrease in SBP (< 15 mmHg), at 9% of the cohort. It is reasonable to focus on this latter group for two reasons. The first is because it is the larger group. Second, there is a

plausible connection between intradialytic hypertension and mortality that can be ameliorated by a simple intervention. This group whose BP hardly decreased may have experienced increased mortality because of volume overload, as intradialytic hypertension has previously been associated with volume excess [10]. Alternatively, the volume overload was recognized by the treating physicians, who prescribed additional ultrafiltration on HD such that they now had SBP decrements during HD and improved mortality. Because the latter analysis was not performed, even big data cannot answer the question.

CONCLUSIONS

When considering how this study may affect clinical practice one must consider several caveats related to the limitations of the design for this retrospective study. Our interpretation is quite different from that of the authors. We conclude that a small decrease in SBP (<15 mmHg from baseline to nadir, averaged over 90 days) should trigger an assessment of volume excess. In those who are volume overloaded, measures to mitigate this volume excess may lead to a greater decline in systolic BP during dialysis, which may associate with better outcomes.

In our opinion, intradialytic hypotension that is clinically relevant (symptomatic, requiring intervention, as defined by the European Best Practice Guidelines) has never been adequately examined, because all big data are samples of convenience. They only collect what the large dialysis organizations have or mandate. If we keep relying on these big data, we will continue to make big mistakes.

Because of the fundamental limitations of retrospective study design, no firm recommendations can be made regarding management of BP on HD beyond the truism that it seems prudent to avoid extremes in BP on HD if possible. As we show above, completely different conclusions can be made from the same data. To be sure, big data by themselves are not good or bad. It is what we do with them, how we interpret them and how we make decisions based on them that makes a difference. Ultimately, prospective studies and randomized controlled trials are necessary to determine whether, when, how and to what extent hypertension

or asymptomatic hypotension on HD should be treated. It is time to plan interventional studies. It is time to rethink.

CONFLICT OF INTEREST STATEMENT

R.A. serves on steering committees for the following companies: Akebia, Johnson & Johnson, Relypsa, Bayer and Boehringer Ingelheim. The other author does not have any conflict of interest to declare.

(See related article by Chou *et al.* Intradialytic hypotension, blood pressure changes and mortality risk in incident hemodialysis patients. *Nephrol Dial Transplant* 2018; 33: 149–159)

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