Kidney Medicine

Intradialytic Hypotension and Mortality in Adolescents and Young Adults With Kidney Failure Receiving Maintenance Hemodialysis

Xixi Zhao, Tara I. Chang, Wolfgang C. Winkelmayer, Jin Long, Sai Liu, and Olivera Marsenic

Rationale & Objective: Intradialytic hypotension (IDH) is associated with mortality in adults with kidney failure requiring hemodialysis (HD); however, large-scale pediatric studies are lacking. Moreover, there is no evidence-based consensus definition of IDH in pediatric literature. We aimed to examine the association of commonly used definitions of IDH with mortality in adolescents and young adults.

Study Design: This was a retrospective observational cohort study.

Setting & Participants: In total, 1,199 adolescents and young adults (N = 320, aged 10-18 years and N = 879, aged 19-21 years) who initiated HD in a large dialysis organization were included.

Exposures: This study used different definitions of IDH.

Outcome: The study outcome was 2-year all-cause mortality.

Analytical Approach: Several definitions of IDH were selected a priori based on a literature review. Patients were classified as having IDH if it was present in at least 30% of HD treatments during the first 90 days after dialysis initiation. Cox proportional hazards regression was used to test whether IDH associated with 2-year all-cause mortality.

Results: Over a 2-year follow-up period, 54 (4.5%) patients died. Dependent on its definition, IDH was present in 2.9%-61.1% of patients. After the multivariable adjustment for sociodemographic and clinical characteristics, we found no association of IDH with mortality. Results were consistent across subgroups stratified by age (aged <18 and 19-21 years) and predialysis systolic blood pressure (<120, 120-150, and >150 mm Hg). We also examined IDH as occurring in <5%, 5%-29%, 30%-50%, and >50% of baseline treatments, and did not find a dose-response association with mortality ($P > 0.05$).

Limitations: Owing to low event rates, our current sample size may have been too small to detect a difference in mortality.

Conclusions: Our study found that IDH was not associated with mortality in adolescents and young adults.

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Intradialytic hypotension (IDH) is a common and serious event among children with kidney failure receiving hemodialysis (HD).[1] In adults, IDH is known to have associations with a range of adverse consequences, including shortened dialysis sessions, resulting in inadequate fluid removal and solute clearance, loss of residual kidney function, cardiac injury, and death.[2-5] Studies on the association of IDH with adverse consequences in the pediatric HD population, however, are sparse.

Further complicating the issue is the lack of an evidence-based consensus definition of IDH in pediatrics. The Pediatric Continuous Renal Replacement Therapy Workgroup defined IDH as systolic blood pressure (SBP) less than the fifth percentile adjusted for age and sex with associated clinical symptoms, such as abdominal pain, nausea, vomiting, muscle cramps, restlessness, light headedness, syncope, and anxiety.[6] However, information on clinical symptoms and interventions performed during HD is often limited, so IDH is also sometimes defined solely by SBP less than the fifth percentile.[7-9] Other definitions include SBP less than the 50th percentile,[10] a 20- or 30-mm Hg drop from predialysis SBP,[11,12] nadir intradialytic SBP below 90 or 100 mm Hg,[13,14] and combination definitions, such as nadir intradialytic SBP less than 90 mm Hg accompanied with a 20- or 30-mm Hg drop from the patient's predialysis SBP.[15]

In a 2015 study on the various definitions of IDH, Flythe et al[16] demonstrated that absolute nadir SBP of less than 90 mm Hg was associated with mortality, and within the subgroup of patients with predialysis SBP > 160 mm Hg, SBP less than 100 mm Hg was most potently associated with mortality. The study involved adults with an average age of around 60 years. These findings cannot be directly translated to the pediatric population owing to age- and sex-based variability in blood pressure norms. Furthermore, hemodynamic responses to blood pressure variability may differ in children, because they tend to have primary kidney disease, with the most common cause of kidney failure being congenital anomalies of the kidney and urinary tract followed by glomerulonephritis.[17] This stands in contrast with adults requiring HD, whose kidney disease is often the result of diabetes mellitus, which can impair autoregulatory responses to blood pressure.[18]

Given the differences among pediatric and adult populations, which necessitates a study specifically designed for the pediatric patient population, we tested whether IDH was associated with 2-year mortality in adolescent and

PLAIN-LANGUAGE SUMMARY

Intradialytic hypotension (IDH), or hypotension experienced during dialysis, is common among children and young adults with kidney failure requiring hemodialysis. We examined the association of commonly used definitions of IDH with death in adolescents and young adults with kidney failure receiving hemodialysis. Intradialytic hypotension was present in 2.9%-61.1% of patients, depending on the definition, and over a 2-year follow-up period, 4.5% of the patients died. We found no association of IDH with mortality.

young adult patients receiving HD, and if so, which definition of IDH best captured that association.

Table 1. Definitions of Intradialytic Hypotension Selected A Priori

Term	Definition
Fifth percentile[6]	70 + (2 × age)[19]
50th percentile[10]	90 + (2 × age)[19]
20 drop[11]	(pre-HD SBP – nadir intradialytic SBP) > 20 mm Hg
30 drop[12]	(pre-HD SBP – nadir intradialytic SBP) > 30 mm Hg
SBP<90mm Hg[13]	Nadir intradialytic SBP < 90 mm Hg
SBP<100mm Hg[14]	Nadir intradialytic SBP < 100 mm Hg
20 drop+SBP <90mm Hg[15]	(pre-HD SBP – nadir intradialytic SBP) > 20 mm Hg and nadir intradialytic SBP < 90 mm Hg
30 drop+SBP <90mm Hg[15]	(pre-HD SBP – nadir intradialytic SBP) > 30 mm Hg and nadir intradialytic SBP < 90 mm Hg

Abbreviations: HD, hemodialysis; SBP, systolic blood pressure.

METHODS

Study Population and Data Collection

This study was approved by Institutional Review Boards at Stanford University (protocol IRB-17904), and Baylor College of Medicine (protocol H-36408), and is currently active. Data were obtained from the US Renal Data System (USRDS), the national registry for patients with kidney failure,[17] linked with data from the electronic health records of a large dialysis organization in the United States, using a patient-level crosswalk provided by the USRDS Coordinating Center. We identified patients from the USRDS with incident kidney failure who initiated maintenance HD at an age between 10 and 21 years and between January 1, 2006, and October 1, 2011, in all 50 states, including the District of Columbia. Informed consent was waived owing to the use of deidentified information. The baseline period was defined as the interval from dialysis initiation to day 91, which we defined as our index date (Fig S1). We also performed a sensitivity analysis with the baseline period extended to 180 days.

The following information was collected at the time of incident kidney failure: age, sex, insurance information, incident kidney failure year, reported race and ethnicity, and cause of kidney failure. During the 90-day baseline period, we ascertained routinely collected monthly laboratory measurements (ie, hemoglobin, white blood cell count, electrolytes, and serum albumin level), detailed hemodynamic parameters during HD (ie, predialysis SBP, postdialysis SBP, nadir intradialytic BP, and the weight before and after HD), and dialysis-related data (ie, dialysate composition, blood flow, dialysate flow, session length, session frequency, dialyzer type, Kt/V, and urea reduction ratio).

Exposures and Outcomes

Exposures of interest were the different IDH definitions, which were selected a priori based on a literature review (Table 1). SBP less than the 5th and 50th percentile was approximated using formulas provided by the Pediatric Advanced Life Support training materials for children aged 10 years.[19] For patients aged more than 10 years, Pediatric Advanced Life Support recommended the lowest acceptable SBP being 90 mm Hg but had no reference population for this threshold. Instead, our study group applied the provided formulas uniformly for children and young adults aged 10-21 years, which aligned very closely with the 5th and 50th percentile definitions of population-based studies.[20,21] Blood pressure was measured according to the dialysis center's usual practice using a standard automated device before and after the dialysis procedure, and every 30 minutes during the treatment sessions. Only predialysis, postdialysis, and intradialytic nadir blood pressure was available in our data set. We calculated the proportion of sessions with IDH by taking the number of dialysis sessions with the specified IDH definition and dividing by the total number of dialysis sessions during the baseline period. Patients were dichotomized as having IDH if they experienced IDH in at least 30% of the HD sessions during the 90-day baseline period, a threshold supported by previous literature.[22] In a companion analysis, we also examined IDH as <5%, 5%-29%, 30%-50%, and >50% of sessions using the SBP < 5th percentile definition and the SBP < 90 mm Hg definition.

Patients were followed until the date of their death, which was recorded in the USRDS patient file, and censored at the time of kidney transplant, after 2 years of follow-up, on September 30, 2013, whichever came first. The outcome of interest was time to death in a 2-year window.

Statistical Analysis

We present continuous data as means and standard deviations, and dichotomous data are reported as counts and proportions. We analyzed the differences in continuous and categorical variables between groups using the t test and χ^2 test, respectively, and considered a 2-sided P value of <0.05 as statistically significant. Further, we examined

2-year survival by the presence of IDH using survival curves generated by the Kaplan-Meier method.[23] Multivariable Cox proportional hazards regression was also applied to evaluate the association between IDH and 2-year survival. The model was adjusted for age, sex, race, and cause of kidney failure. Survival analysis and multivariable Cox proportional hazards were conducted with various definitions of IDH, using the SBP value (<90 mm Hg and <100 mm Hg), percentile (<5th and <50th percentile), and drop in SBP (20 mm Hg and 30 mm Hg). All statistical analyses were performed with R version 4.2.2 (R Foundation for Statistical Computing; www.R-project.org).

RESULTS

Fig 1 shows the cohort selection across key steps. Patients were included if they had 5 or more HD sessions within the first 45 days of their first HD treatment. The study population was further restricted to patients who had 20 or more blood pressure measurements recorded in the first 5 HD sessions. Patients who died, received a kidney transplant, or received any peritoneal dialysis treatments were excluded. The final study population included 1,199 patients, whose characteristics are shown in Table 2. The average age was 19.1 ± 2.1 years, median age was 20 years, and interquartile range (IQR) was 18-21. There were 320 patients aged 10-18 years (median, 17 years; IQR, 16-18) and 879 patients aged 19-21 years (median, 20 years; IQR, 19-21). Compared with patients who did not meet the definition for SBP < 90 mm Hg, patients who met the definition for SBP < 90 mm Hg were more likely to be younger and of the female sex. During the 90-day baseline period, there were a total of 43,158 HD treatments with 149,025 blood pressure measurements, which translates to a mean of 36 HD treatments and 124 blood pressure measurements per patient. Over a 2-year follow-up period, 54 (4.5%) patients died (Table S1). Within the group of patients who died, 9 were aged 10-18 years and 45 were aged 19-21 years.

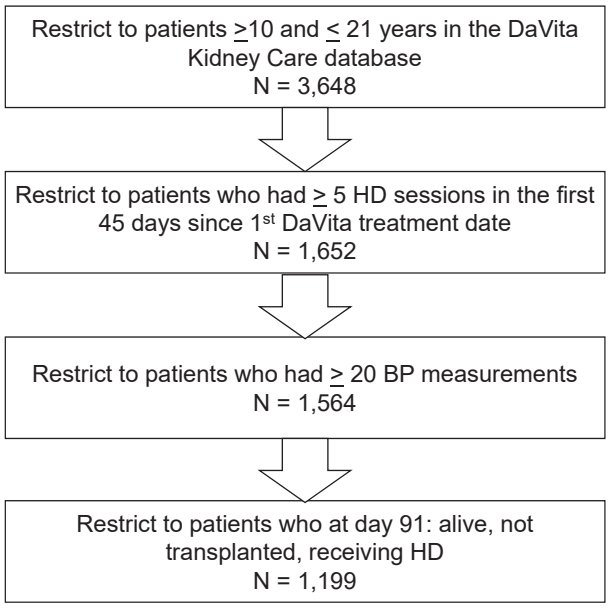

Figure 1. A flow diagram of cohort selection. BP, blood pressure; HD, hemodialysis.

The frequency of IDH varied by the definition used, ranging from 2.9%-61.1% (Fig 2). Fig S2 demonstrates the frequency of IDH stratified by age groups. In adjusted analyses, none of the IDH definitions had significant associations with 2-year mortality (Fig 3). A separate sensitivity analysis with the baseline exposure period extended to 180 days did not find an independent association of IDH with 2-year mortality either (Fig S3). Subgroup analysis by age (<18 and 19-21 years old) and predialysis SBP (<120, 120-150, and >150 mm Hg) did not demonstrate a relationship with 2-year mortality (Tables 3 and 4, respectively). We then examined the occurrence of IDH in <5%, 5%-29%, 30%-50%, and >50% of baseline HD treatments, and we did not find a dose-response association of IDH with 2-year mortality. Fig 4 shows the dose-response association of IDH with SBP < fifth percentile and SBP < 90 mm Hg.

Combination definitions, including both SBP < 90 mm Hg accompanied with a 20-mm Hg drop as well as SBP < 90 mm Hg accompanied with a 30-mm Hg drop had no deaths in the exposure group (Table S2). Therefore, they were excluded from subgroup analyses owing to the inadequate number of events in the IDH group, which would have produced unreliable prediction models.

DISCUSSION

In a large cohort of 1,199 adolescents and young adults initiating HD for kidney failure, we found that none of the commonly used definitions of IDH was associated with mortality, contrary to previous findings in adults.[16] The lack of an evidence-based definition of IDH for pediatric patients makes it difficult to assess the mechanisms underlying blood pressure regulation during HD that lead to IDH, the adverse consequences of IDH, and importantly, treatment and prevention strategies for IDH. Therefore, finding a consistent, evidence-based definition for IDH is an imperative first step. Several conclusions could arise from this finding.

One explanation is that children requiring maintenance HD are healthier at baseline than their adult counterparts. According to the USRDS, mortality in the first 2 years of HD for children is 6% compared with 32% in adults.[17] More adult patients withdraw from dialysis than children, but even after adjusting for withdrawal rates, mortality in adults remains more than double that of children.[24,25] Although cardiovascular mortality accounts for the majority of deaths in both age cohorts, adult patients have a far greater cardiovascular comorbid condition burden. Using data from the Hemodialysis Study, Cheung

Table 2. Baseline Characteristics

Characteristic	Patients Meeting SBP < 90 mm Hg IDH Definition (N = 27)	Patients Not Meeting SBP < 90 mm Hg IDH Definition (N = 1,172)
Age (y), n (%)	18.3 + 3.2	19.1 + 2.0
10-18	10 (37.0)	310 (26.4)
19-21	17 (63.0)	862 (73.6)
Female sex, n (%)	14 (51.8)	485 (41.4)
Race, n (%)		
Asian	1 (3.7)	45 (3.8)
African American	8 (29.6)	402 (34.3)
White	12 (44.4)	340 (29.0)
Hispanic	5 (18.5)	341 (29.1)
Other	1 (3.7)	44 (3.8)
Insurance, n (%)		
Group Health Organization	0 (0)	63 (5.4)
Medicare as primary payer	17 (62.9)	664 (56.6)
Medicare as secondary payer	1 (3.7)	88 (7.5)
Other or unknown	9 (33.3)	357 (30.5)
Cause of kidney failure, n (%)		
CAKUT	6 (22.2)	112 (9.6)
Glomerulonephritis	10 (37.0)	460 (39.2)
Genetic	0 (0)	10 (0.8)
Other	6 (22.2)	301 (25.7)
Unknown	5 (18.5)	289 (24.7)
Dialysis-related parameters		
Dialysate potassium (mmol/L)	2.1 + 0.5	2.1 + 0.4
Dialysate bicarbonate (mmol/L)	36 + 2	37 + 3
Dialysate calcium (mmol/L)	2.4 + 0.2	2.4 + 0.2
Predialysis temperature (F)	96.9 + 0.8	97.0 + 0.9
Postdialysis temperature (F)	97.2 + 0.6	97.2 + 0.6
Ultrafiltration rate (mL/h/kg)	11.5 + 5.5	12.1 + 10.6
Predialysis SBP (mm Hg)	125 + 15	148 + 17
Urea reduction ratio (%)	72 + 7.0	70 + 7.5
Kt/V	1.9 + 0.3	1.8 + 0.5
Laboratory studies		
Sodium (mmol/L)	140 + 3	140 + 2
Potassium (mmol/L)	4.4 + 0.6	4.7 + 0.6
Chloride (mmol/L)	99 + 5	101 + 4
Bicarbonate (mmol/L)	23 + 3	23 + 3
Serum urea nitrogen (mg/dL)	51 + 12	53 + 15
Creatinine (mg/dL)	9.3 + 3.3	9.9 + 3.4
Albumin (g/dL)	3.9 + 0.5	3.9 + 0.5
Alkaline phosphatase (U/L)	184 + 194	114 + 109
Calcium (mg/dL)	9.2 + 0.7	8.9 + 0.7
Phosphorus (mg/dL)	6.0 + 1.8	6.1 + 1.5
Intact PTH (pg/dL)	625 + 586	615 + 582
White blood cell (g/dL)	6.6 + 2.5	7.3 + 2.3
Hemoglobin (g/dL)	11.4 + 1.1	11.2 + 1.3
Hematocrit (%)	35 + 3.2	35 + 3.8
Platelet count (K/μL)	243 + 72	248 + 77
Iron (mg/dL)	62 + 26	61 + 24
Ferritin (ng/mL)	427 + 304	376 + 402
Low-density lipoprotein (mg/dL)	68 + 37	85 + 42
Cholesterol (mg/L)	148 + 45	161 + 57
Triglyceride (mg/L)	135 + 60	172 + 73

Abbreviations: CAKUT, congenital anomalies of the kidney and urinary tract; IDH, intradialytic hypotension; PTH, parathyroid hormone; SBP, systolic blood pressure.

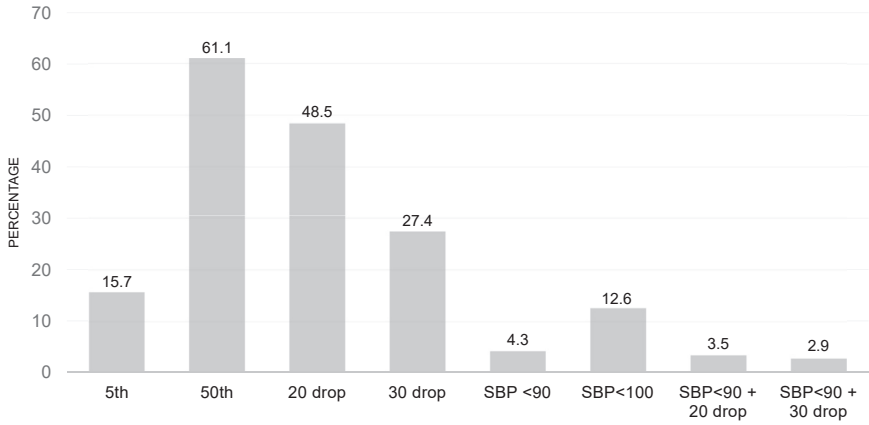

Figure 2. The frequency of IDH for the selected IDH definitions. Frequency is defined by the number of dialysis sessions meeting the specified IDH definition divided by the total number of dialysis sessions during the baseline period. IDH, intradialytic hypotension.

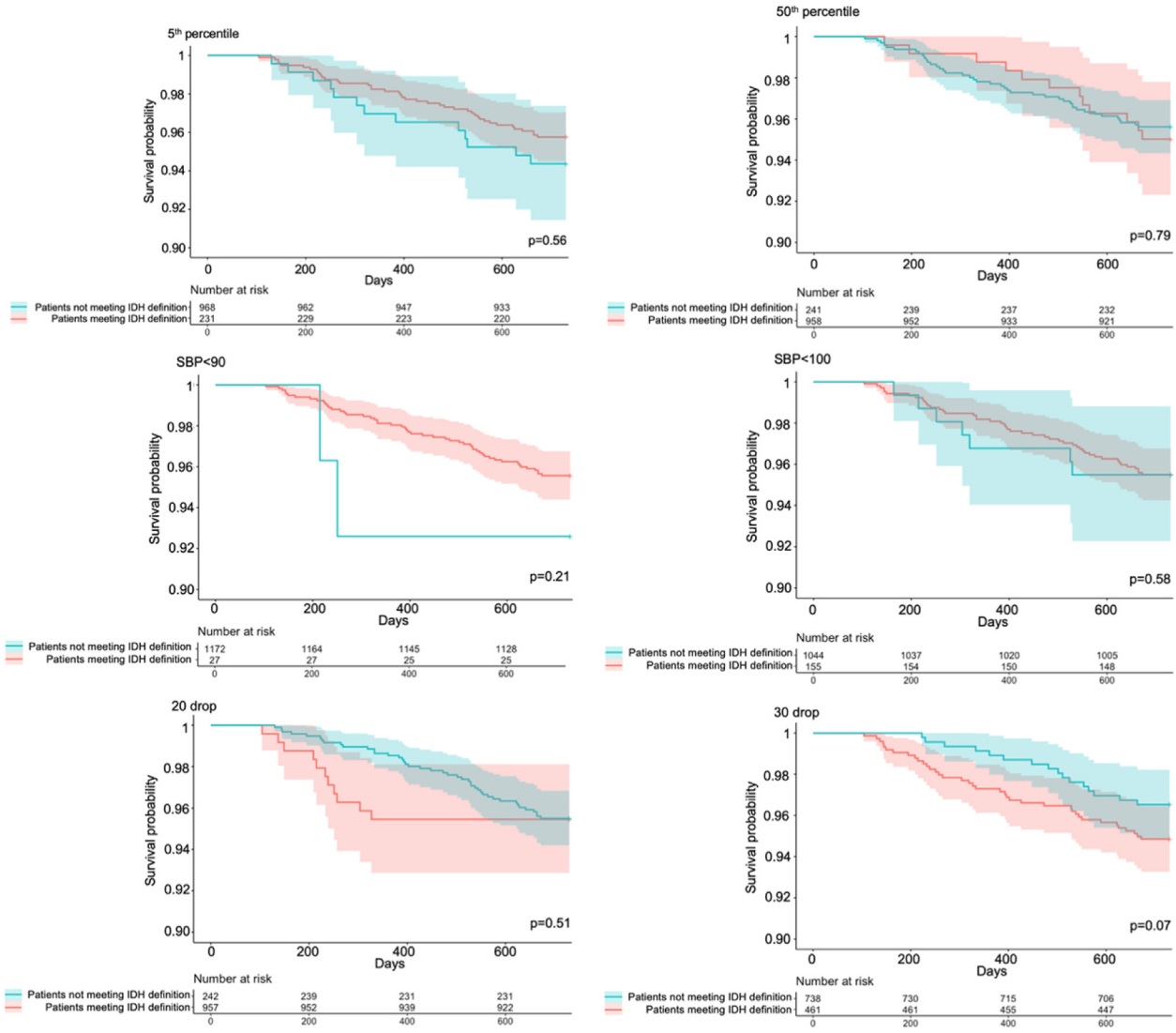

Figure 3. Adjusted survival curves. Compound definitions of SBP < 90 mm Hg + 20 drop and SBP < 90 mm Hg + 30 drop were excluded from the analysis owing to an inadequate number of events in the IDH group to produce a reliable prediction model. All analyses were adjusted for age, sex, race, and cause of kidney failure. IDH, intradialytic hypotension; SBP, systolic blood pressure.

Table 3. Subgroup Analysis by Age (<18 and >19 Years Old)

Definition	Age Group	Adjusted Hazard Ratios
Fifth percentile	≤18 years	1.84 (0.31-10.75)
	≥19 years	1.11 (0.55-2.26)
50th percentile	≤18 years	2.99 (0.34-26.57)
	≥19 years	0.84 (0.40-1.75)
20 drop	≤18 years	0.69 (0.14-3.42)
	≥19 years	0.88 (0.39-1.94)
30 drop	≤18 years	1.44 (0.29-6.95)
	≥19 years	0.49 (0.25-0.96)
SBP<90mm Hg	≤18 years	10.98 (0.35-344.89)
	≥19 years	1.27 (0.16-10.08)
SBP<100mm Hg	≤18 years	2.51 (0.34-18.38)
	≥19 years	1.09 (0.42-2.87)

Note: Compound definitions of SBP < 90 mm Hg + 20 drop and SBP < 90 mm Hg + 30 drop were excluded from the analysis owing to an inadequate number of events in the IDH group to produce a reliable prediction model.
Abbreviations: IDH, intradialytic hypotension; SBP, systolic blood pressure.

Table 4. Subgroup Analysis Based on Predialysis SBP (<120, 120-150, and >150 mm Hg)

Definition	Predialysis SBP (mm Hg)	Adjusted Hazard Ratios
Fifth percentile	SBP < 120	1.09 (0.56-2.17)
	SBP 120-150	1.26 (0.64-2.48)
	SBP > 150	1.19 (0.59-2.41)
50th percentile	SBP < 120	0.86 (0.44-1.71)
	SBP 120-150	0.94 (0.43-2.01)
	SBP > 150	0.81 (0.36-1.83)
20 drop	SBP < 120	0.86 (0.42-1.74)
	SBP 120-150	0.80 (0.39-1.61)
	SBP > 150	0.82 (0.41-1.67)
30 drop	SBP < 120	0.59 (0.32-1.09)
	SBP 120-150	0.55 (0.29-1.02)
	SBP > 150	0.56 (0.29-1.05)
SBP<90mm Hg	SBP < 120	1.95 (0.39-9.65)
	SBP 120-150	2.49 (0.55-11.26)
	SBP > 150	2.44 (0.53-11.20)
SBP<100mm Hg	SBP < 120	0.95 (0.35-2.60)
	SBP 120-150	1.26 (0.55-2.92)
	SBP > 150	1.22 (0.51-2.91)

Note: Compound definitions of SBP < 90 mm Hg + 20 drop and SBP < 90 mm Hg + 30 drop were excluded from analysis owing to an inadequate number of events in the IDH group to produce a reliable prediction model.
Abbreviations: IDH, intradialytic hypotension; SBP, systolic blood pressure.

et al[26] found that 80% of adult dialysis patients had cardiac diseases at baseline, including 39% with ischemic heart disease, 40% with congestive heart failure, and 31% with arrhythmias. The study concluded that any cardiac disease was highly predictive of cardiac death during follow-up.[26] Children with kidney failure have higher prevalence rates of hypertension, left ventricular hypertrophy, and dyslipidemia compared with any other pediatric patient populations, but they rarely have symptomatic coronary artery disease.[27] Their cardiovascular burden often reflects the sequelae of chronic kidney disease alone compared with older adults, who tend to reflect both the consequences of the uremic milieu in addition to chronic damage incurred from other comorbid conditions, commonly diabetes and long-standing hypertension. With a poorer cardiac substrate at baseline, the aged myocardium may be particularly vulnerable to recurrent ischemic hypotensive episodes, leading to a higher 2-year mortality rate post HD initiation. Based on the hypothesis that the younger and healthier myocardium may require a longer duration of ischemic insult before seeing a signal for 2-year mortality, we conducted a separate analysis with the baseline exposure extended to 180 days. The result remained essentially unchanged with an additional 90 days used for IDH exposure ascertainment; we did not find an independent association of IDH with 2-year mortality. Again, this finding continues to suggest the resilience of the younger and relatively healthier myocardium to hypotension.

Another explanation is that the current definitions of IDH are not optimal for the pediatric population. The use of SBP less than the 5th and 50th percentile originated from the pediatric literature based on population-based cross-sectional studies of healthy children and adolescents.[20,21] Although having a blood pressure measurement under the fifth percentile may span one extreme of the Gaussian curve, it is still considered a normal blood pressure measurement for 5% of healthy children and adolescents. Therefore, using percentile definitions in pathologic states such as kidney failure may overestimate the true incidence of hypotension in our population of interest. It is also interesting to note that our subgroup analyses based on age did not yield a statistically significant association between SBP < 90 mm Hg or SBP < 100 mm Hg and mortality in the young adult group aged 19-21 years. In both adult and pediatric medicine, this age group would be clinically regarded as adults, and one would expect that the findings from Flythe et al[16] would be replicated in this age cohort. However, there is emerging evidence that young adults are more biologically similar to pediatric patients than they are to adults. For example, pediatric estimated glomerular filtration rate (eGFR) equations tend to approximate closer with the measured GFR by inulin in young adults than adult formulas.[28] Recently, a new pediatric eGFR equation was introduced and allowed the calculation of eGFR for young adult patients up to the age of 25 years.[29] In oncology, there is a movement to place young adults with blood cancers on pediatric-inspired regimens rather than on adult regimens, given a more favorable outcome with the former treatment.[30]

Contrary to our hypothesis, stratified analyses based on predialysis SBP similarly did not yield a statistically significant association between any of the IDH definitions and mortality. This result may suggest that adolescents and young adults have a compensatory mechanism far more robust than that of adults, in which a higher SBP or blood volume reduction needs to be reached before coronary ischemia ensues. This may also explain why the 20 mm Hg- and 30 mm Hg-drop definitions did not associate with mortality either. One other finding to support the aforementioned hypothesis is a retrospective study on ultrafiltration rates used during HD for 1,592 children and

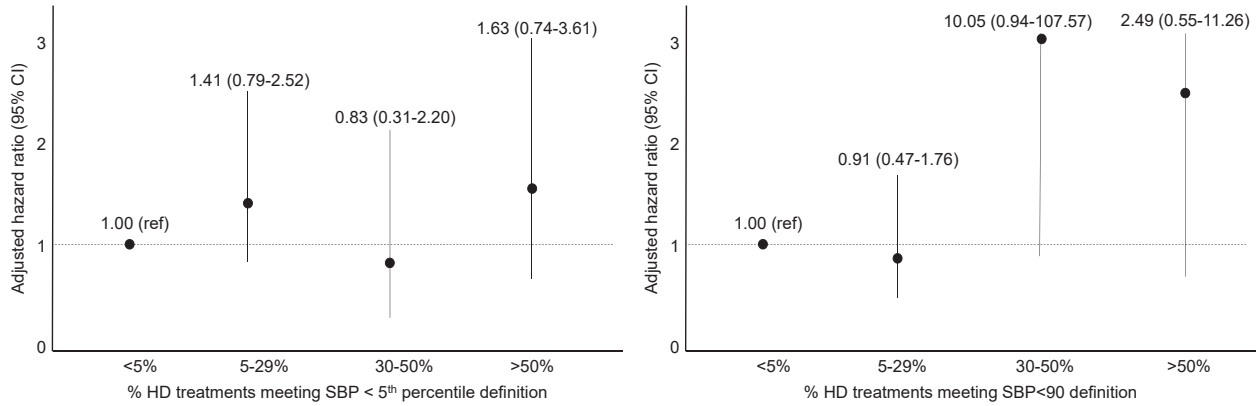

Figure 4. Analyses using categories of IDH episode frequency. Analyses were adjusted for age, sex, race, and cause of kidney failure. IDH, intradialytic hypotension.

adolescents aged 1-18 years. Gotta et al[31] demonstrated that ultrafiltration rates in children frequently exceeded the adult upper limit recommendation of 13 mL/kg/h in 17.6%, 27.9%, 45.8%, and 29.2% of the time in patients aged 1-2 years, 3-5 years, 6-11 years, and 12-18 years, respectively. In a follow-up study, a higher ultrafiltration rate up to 18 mL/kg/h was not associated with mortality.[32] The pediatric literature reports that a 10% blood volume reduction over a 3-hour session or up to 8% body weight reduction is well tolerated.[33] This translates to an ultrafiltration rate of 26 mL/kg/h in a 25-kg child. Indeed, there appears to be a higher tolerance and better compensatory response for fluid removal in pediatric patients.

Our study has several strengths, including the use of a large representative cohort of US pediatric patients initiating HD and 8 different IDH definitions from both the adult and pediatric literature. Another major strength of our study is the use of a patient population that is derived from a single large dialysis organization, because practice patterns may vary greatly from one pediatric institution to another. The advantage of being exposed to a homogenous practice ensures that all study participants are treated consistently across the nation, including the use of similar blood pressure monitors, HD machines, and laboratories for blood sample processing. Our study also has several notable limitations. First, owing to low event rates, our current sample size may have been too small to detect a difference in mortality, and future studies should confirm our findings with a larger sample size. Second, for our results to be comparable to those showing the association of IDH with mortality in adults, we used a similar methodology, exposures, and outcomes as the study published by Flythe et al,[16] although using Cox rather than logistic regression (when using logistic regression, the findings remained essentially unchanged). Consequently, we did not extend the baseline exposure period to greater than 180 days or extend the 2-year follow-up period. Doing so would also decrease our sample size and would have resulted in less reliable prediction models. Third, patients who had longer exposure to the uremic milieu are more likely to have accelerated coronary artery disease as a result and may be more vulnerable to IDH, but we did not have available data on the duration of chronic kidney disease before HD initiation and, therefore, could not have accounted for these covariates in our prediction models. Fourth, the use of pediatric formulas to approximate the 5th and 50th percentile SBP for adult patients aged 18-21 years may have overestimated their true SBP. However, no comprehensive study has been conducted on blood pressure percentiles in adults in the United States. One study constructed blood pressure percentiles in Iranian adults, but their youngest patients were aged 25 years.[34] Fifth, the hemodynamic changes throughout a patient's dialysis experience were reduced to several blood pressure data points during a single HD treatment and may not provide enough information to reflect end-organ damage. Alternative measures that evaluate continuous blood pressure changes or the trajectory of blood pressure changes during dialysis treatments can be explored in future studies. Finally, we also did not have available data on symptoms and interventions performed during HD to assess symptom- and intervention-based IDH definitions.

In conclusion, contrary to prior adult studies, IDH was not independently associated with mortality in adolescent and young adult patients in a large national sample of the said population initiating HD in the United States. Future studies should confirm our findings in view of the limitations of our study. Future studies should also explore other IDH definitions with mortality and examine the association of IDH with outcomes other than death as well as mechanisms that may allow this population to better tolerate IDH.

SUPPLEMENTARY MATERIAL

Supplementary File 1 (PDF)

Figure S1: Study timeline.

Figure S2: Frequency of IDH for the selected IDH definitions with subgroup analysis by age (10-18 years old and 19-21 years old).

Figure S3: Adjusted survival curves extended to 180 days.

Table S1: Comparison of Survival and Death Rates According to Baseline Characteristics, Dialysis-Related Parameters, and Laboratory Studies.

Table S2: Survival and Death Rates in Patients Meeting Selected IDH Definitions Versus not Meeting Selected IDH Definitions.

ARTICLE INFORMATION

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REFERENCES

1. Hayes W, Hothi DK. Intradialytic hypotension. *Pediatr Nephrol*. 2011;26(6):867-879.
2. Shoji T, Tsubakihara Y, Fujii M, Imai E. Hemodialysis associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. *Kidney Int*. 2004;66(3):1212-1220.
3. Rees L, Schaefer F, Schmitt CP, Shroff R, Warady BA. Chronic dialysis in children and adolescents: challenges and outcomes. *Lancet Child Adolesc Health*. 2017;1(1):68-77.
4. Lee YJ, Okuda Y, Sy J, et al. Ultrafiltration rate, residual kidney function, and survival among patients treated with reduced-frequency hemodialysis. *Am J Kidney Dis*. 2020;75(3):342-350.
5. Stefánsson BV, Brunelli SM, Cabrera C, et al. Intradialytic hypotension and risk of cardiovascular disease. *Clin J Am Soc Nephrol*. 2014;9(12):2124-2132.
6. Raina R, Lam S, Raheja H, et al. Pediatric intradialytic hypotension: recommendations from the Pediatric Continuous Renal Replacement Therapy (PCRRT) Workgroup. *Pediatr Nephrol*. 2019;34(5):925-941.
7. Merouani A, Kechaou W, Litalien C, Ducruet T, Jouvet P. Impact of blood volume monitoring on fluid removal during intermittent hemodialysis of critically ill children with acute kidney injury. *Nephrol Dial Transplant*. 2011;26(10):3315-3319.
8. Hothi DK, Harvey E, Goia CM, Geary DF. Evaluating methods for improving ultrafiltration in pediatric hemodialysis. *Pediatr Nephrol*. 2008;23(4):631-638.
9. Hothi DK, Harvey E, Goia CM, Geary D. Blood-volume monitoring in paediatric haemodialysis. *Pediatr Nephrol*. 2008;23(5):813-820.
10. Marsenic O, Anderson M, Couloures KG, Hong WSH, Dahl N. Effect of the decrease in dialysate sodium in pediatric patients on chronic hemodialysis. *Hemodial Int*. 2016;20(2):277-285.
11. Dubin R, Owens C, Gasper W, Ganz P, Johansen K. Associations of endothelial dysfunction and arterial stiffness with intradialytic hypotension and hypertension. *Hemodial Int*. 2011;15(3):350-358.
12. Blowey DL, Balfe JW, Gupta I, Gajaria MM, Koren G. Midodrine efficacy and pharmacokinetics in a patient with recurrent intradialytic hypotension. *Am J Kidney Dis*. 1996;28(1):132-136.
13. Oliver MJ, Edwards LJ, Churchill DN. Impact of sodium and ultrafiltration profiling on hemodialysis-related symptoms. *J Am Soc Nephrol*. 2001;12(1):151-156.
14. Zhou YL, Liu HL, Duan XF, Yao Y, Sun Y, Liu Q. Impact of sodium and ultrafiltration profiling on haemodialysis-related hypotension. *Nephrol Dial Transplant*. 2006;21(11):3231-3237.
15. Imai E, Fujii M, Kohno Y, et al. Adenosine A1 receptor antagonist improves intradialytic hypotension. *Kidney Int*. 2006;69(5):877-883.
16. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol*. 2015;26(3):724-734.
17. United States Renal Data System. *2020 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2020.
18. Chesterton LJ, Selby NM, Burton JO, Fialova J, Chan C, McIntyre CW. Categorization of the hemodynamic response to hemodialysis: the importance of baroreflex sensitivity. *Hemodial Int*. 2010;14(1):18-28.
19. Kleinman ME, Chameides L, Schexnayder SM, et al. Part 14: pediatric advanced life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122(18 Suppl 3):S876-S908.
20. Sarganas G, Rosario AS, Berger S, Neuhauser HK. An unambiguous definition of pediatric hypotension is still lacking: gaps between two percentile-based definitions and Pediatric Advanced Life Support/Advanced Trauma Life Support guidelines. *J Trauma Acute Care Surg*. 2019;86(3):448-453.

21. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140(3):e20171904.
22. Chang TI, Paik J, Greene T, et al. Intradialytic hypotension and vascular access thrombosis. *J Am Soc Nephrol*. 2011;22(8):1526-1533.
23. Jager KJ, Van Dijk PC, Zoccali C, Dekker FW. The analysis of survival data: the Kaplan–Meier method. *Kidney Int*. 2008;74(5):560-565.
24. Bradbury BD, Fissell RB, Albert JM, et al. Predictors of early mortality among incident US hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Clin J Am Soc Nephrol*. 2007;2(1):89-99.
25. Chesnaye NC, Schaefer F, Groothoff JW, et al. Mortality risk in European children with end-stage renal disease on dialysis. *Kidney Int*. 2016;89(6):1355-1362.
26. Cheung AK, Sarnak MJ, Yan G, et al. Cardiac diseases in maintenance hemodialysis patients: results of the HEMO Study. *Kidney Int*. 2004;65(6):2380-2389.
27. Mitsnefes MM. Cardiovascular disease in children with chronic kidney disease. *J Am Soc Nephrol*. 2012;23(4):578-585.
28. Selistre L, De Souza V, Cochat P, et al. GFR estimation in adolescents and young adults. *J Am Soc Nephrol*. 2012;23(6):989-996.
29. Pierce CB, Muñoz A, Ng DK, Warady BA, Furth SL, Schwartz GJ. Age-and sex-dependent clinical equations to estimate glomerular filtration rates in children and young adults with chronic kidney disease. *Kidney Int*. 2021;99(4):948-956.
30. Siegel SE, Stock W, Johnson RH, et al. Pediatric-inspired treatment regimens for adolescents and young adults with philadelphia chromosome–negative acute lymphoblastic leukemia: a review. *JAMA Oncol*. 2018;4(5):725-734.
31. Gotta V, Pfister M, Marsenic O. Ultrafiltration rates in children on chronic hemodialysis routinely exceed weight based adult limit. *Hemodial Int*. 2019;23(1):126-128.
32. Gotta V, Marsenic O, Atkinson A, Pfister M. Hemodialysis (HD) dose and ultrafiltration rate are associated with survival in pediatric and adolescent patients on chronic HD—a large observational study with follow-up to young adult age. *Pediatr Nephrol*. 2021;36(8):2421-2432.
33. Gotta V, Marsenic O, Pfister M. Age- and weight-based differences in haemodialysis prescription and delivery in children, adolescents and young adults. *Nephrol Dial Transplant*. 2018;33(9):1649-1660.
34. Hosseini M, Baikpour M, Yousefifard M, et al. Blood pressure percentiles by age and body mass index for adults. *EXCLI J*. 2015;14:465-477.