Ambient temperature and the occurrence of intradialytic hypotension in patients receiving hemodialysis

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Running head: Ambient temperature and risk of IDH
Ambient temperature and the occurrence of intradialytic hypotension in patients receiving hemodialysis

Intradialytic hypotension (IDH) is a common complication in hemodialysis. Despite understanding the impact of ambient temperature on fluid removal and pre-dialysis blood pressure, its connection to IDH remains under-researched.

**Methods**
- 110,400 sessions
- 182 ESKD patients in Taiwan
- GPS-matched
- PreHD 24 hr
- Mean ambient temperature
- Intradialytic hypotension (IDH)
  - Fall40, Nadir90/100
- Logistic regression with generalized estimating equation

**Results**
- Threshold of 27°C
- Ultrafiltration mediates about 23% of the IDH risk linked to lower temperatures
- Every ↓4°C below threshold 27°C:
  - Fall40 IDH ↑29%
  - Nadir90/100 IDH ↑21%

**Conclusion:** Lower ambient temperature is significantly associated with an increased risk of IDH below the threshold of 27°C, irrespective of the IDH definition used.

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ABSTRACT

Background.

Intradialytic hypotension (IDH) is a common hemodialysis complication causing adverse outcomes. Despite the well-documented associations of ambient temperatures with fluid removal and pre-dialysis blood pressure, the relationship between ambient temperature and IDH has not been adequately studied.

Methods.

We conducted a cohort study at a tertiary hospital in southern Taiwan between January 1, 2016 and October 31, 2021. The 24-hour pre-hemodialysis mean ambient temperature was determined using hourly readings from the weather station closest to each patient's residence. IDH was defined using Fall40 (systolic BP drop of ≥ 40mmHg) or Nadir90/100 (systolic BP <100 if pre-dialysis systolic BP was ≥ 160, or systolic BP <90 mmHg). Multivariate logistic regression with generalizing estimating equations and mediation analysis were utilized.

Results.

The study examined 110,400 hemodialysis sessions from 182 patients, finding an IDH prevalence of 11.8% and 10.4% as per the Fall40 and Nadir90/100 criteria. It revealed a reverse J-shaped relationship between ambient temperature and IDH, with a turning point around 27°C. For temperatures under 27°C, a 4°C drop significantly increased the odds ratio of IDH to 1.292 (95% confidence interval (CI) 1.228 to 1.358) and 1.207 (95% CI 1.149 to 1.268) under the Fall40 and Nadir90/100 definitions, respectively. Lower ambient temperatures correlated with higher ultrafiltration, accounting for
about 23% of the increased IDH risk. Stratified seasonal analysis indicated that this relationship was consistent in spring, autumn, and winter.

Conclusion.

Lower ambient temperature is significantly associated with an increased risk of IDH below the threshold of 27°C, irrespective of the IDH definition. This study provides further insight into environmental risk factors for IDH in patients undergoing hemodialysis.

KEY LEARNING POINTS

What was known:

1. Intradialytic hypotension (IDH) is recognized as a common and potentially fatal complication during hemodialysis, yet there is no consensus on its definition.

2. Ambient temperatures are linked to blood pressure and ultrafiltration, both closely related to IDH, though not conclusively studied in this context.

This study adds:

1. The research demonstrates a reverse J-shaped relationship between ambient temperature and IDH, identifying approximately 27°C as a critical threshold, consistent across multiple IDH definitions.

2. Below 27°C, each 4°C decrease in temperature is associated with up to a 29% increased risk of IDH.

3. Lower temperatures before hemodialysis are associated with higher ultrafiltration, which mediates 23% of the cold temperature's impact on IDH.
Potential impact:

1. Clinicians should consider environmental temperature as a factor in the care of hemodialysis patients and utilize optimal fluid management to partially mitigate cold-related IDH.

2. Coping strategies and physiological mechanisms underlying low-temperature risks necessitate further research as they are critical to understanding and addressing IDH.

Keywords: ambient temperature, hemodialysis, intradialytic hypotension, seasonal variation, threshold
INTRODUCTION

As climate change intensifies heat and cold, evaluating the potential health impacts of temperature exposure is crucial. [1, 2]. Ambient temperature has been linked to an increased risk of cardiovascular morbidity and mortality [3-7]. Literature has reported that patients with End-Stage Kidney Disease (ESKD) are susceptible to the hazards of temperature exposure [8, 9], partly relating to their high burden of cardiovascular disease and comorbidities [10].

Intradialytic hypotension (IDH), a common complication of hemodialysis, is associated with vascular access dysfunction [11], inadequate hemodialysis [12], morbidities [13-15], and mortality [13, 14, 16, 17]. Identification of associated risk factors is vital for improved patient care [14, 18-21]. However, the potential impact of ambient temperature on IDH remains understudied, despite these patients being particularly vulnerable to temperature challenges.

Cold temperatures affect blood pressure and water balance, with prior studies showing dialysis patients in cold conditions have more fluid removal (ultrafiltration) and vasoconstriction [22, 23]. This leads to higher pre-dialysis blood pressure and a diminished ability to counter fluid deficits, potentially causing IDH [22, 24].

Moreover, vasoconstriction may increase the heart's workload and oxygen demand, potentially disrupting steady circulation in susceptible patients [25]. Although low temperatures are linked to high ultrafiltration and higher pre-dialysis blood pressure - both risk factors for IDH - studies investigating the impact of ambient temperature on IDH are limited. Furthermore, previous studies on the health effects of temperature had methodological weaknesses. For example, they used ambient temperature data from a single weather
station near the hemodialysis center or nearby airport, which may not accurately reflect patients’ actual residential temperature exposure [8, 9, 22, 26, 27].

In this study, we examined the association between 24-hour mean ambient temperature obtained from GPS-matched weather stations prior to each hemodialysis session. The objectives of the analysis were to (1) examine the correlation between ambient temperature and IDH; (2) determine if there is a threshold ambient temperature associated with IDH; (3) identify the IDH definition most relevant to ambient temperature; and (4) investigate any potential seasonal variations in this association. Findings from this study would contribute to understanding the potential influence of ambient temperature on IDH, which may aid in developing interventions to ameliorate the adverse effects of low temperatures on patients undergoing hemodialysis.

**MATERIALS AND METHODS**

**Study Design**

The Assessing Temperature Effect on Hemodialysis (ATEMPT-HD) study was an observational cohort study designed to investigate the association between temperature and hemodialysis outcomes. The study was conducted at the hemodialysis center of National Cheng Kung University Hospital, a tertiary teaching hospital in Tainan, Taiwan. In the study period between January 1st, 2016 and October 31st, 2021, a total of 190 patients underwent dialysis. Of these, 182 patients (95.8%) were included in the study analysis, including 17 deceased patients. Written informed consent was obtained from all living patients. The study was approved by the Institutional Review Board of National...
Cheng Kung University Hospital (A-ER-110-327) and adhered to the principles of the Declaration of Helsinki. The number of patients and the corresponding number of hemodialysis sessions are depicted in Figure 1a.

**Temperature Assessment**

We obtained hourly ambient temperature measurements from the Central Weather Bureau (CWB) of Taiwan (https://opendata.cwb.gov.tw). The address of each patient’s home was inserted into the Global Positioning System (GPS) and coordinated according to its latitude and longitude. The closest weather station was determined based on the shortest great circle distance, calculated using the Haversine formula [28]. Temperature data was obtained from the weather station nearest to the patient’s address (Figure 1b). A total of 56 weather stations were affiliated with CWB in southern Taiwan (the study area), and 21 of them provided temperature readings for this study (Table S1). We extracted the hourly temperature records for the 24 hours preceding each hemodialysis session and calculated the mean ambient temperature over this period (i.e., Pre-HD 24-hour mean ambient temperature). The selection of 24 hours is based on literature, which has shown cold temperatures impact mortality with the strongest association on the same day [29]. Temperature distribution during hemodialysis sessions is shown in Figure 2a and by season in Figure 2b. IDH prevalence is also depicted based on specific temperatures.

**Determination of IDH**

The determination of intradialytic hypertension (IDH) was based on multiple criteria in the primary and sensitivity analyses. We adopted the
reduction-based criteria (Fall40), which defines IDH as a reduction in systolic blood pressure (SBP) of ≥40 mmHg (Pre-HD SBP minus minimum SBP, ≥40 mmHg). We also used the nadir-based criteria (Nadir90/100), which defines IDH as the occurrence of intradialytic SBP <90 mmHg in patients with a pre-HD SBP <160 mmHg or SBP <100 mmHg in patients with a pre-HD SBP ≥160 mmHg. Moreover, we conducted sensitivity analyses with another five definitions of IDH to confirm the temperature-IDH relationship. Detailed definitions of IDH are shown in Table S2. Blood pressure was measured before and every 60 minutes during hemodialysis, resulting in at least five records per four-hour session. Each session was then classified as either IDH or non-IDH. The prevalence of IDH according to the definitions of IDH is shown in Table S2.

Clinical Covariates and Dialysis Records

Clinical covariates were collected and categorized into three groups: demographic and comorbidity information, hemodialysis records of each session, and antihypertensive medications. Demographic and comorbidity data, such as age, sex, diabetes mellitus, hypertension, coronary artery disease, Charlson Comorbidity Index (CCI) [30] were obtained by reviewing patient medical charts. Hemodialysis records of each session included information such as HD vintage (months), pre-HD systolic blood pressure (mmHg), pre-HD body weight (kg), dry weight (kg), ultrafiltration weight (kg), blood flow (ml/min), dialysate flow (ml/min), dialysate average temperature (°C), conductivity (dialysate sodium (mEq/L)), dialysate calcium (mEq/L), and monthly hemoglobin; all of which were extracted from the hospital electronic medical records. The ultrafiltration weight to dry weight ratio (UF/DW) was
calculated and presented as a percentage (%). Antihypertensive medications were categorized monthly into five groups: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB), beta-blockers, alpha blockers, calcium channel blockers, and vasodilators. Additionally, data on the use of intravenous iron supplements (IV_iron) were extracted (see Table S3). Under the Taiwan National Health Insurance program, prescriptions for more than one drug in the same category are restricted. Therefore, we coded each category as either present or absent.

**Statistical Analyses**

Data were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) for continuous variables and numbers and percentages for categorical variables. Characteristics of HD sessions were compared using standardized difference, a measure that is not sensitive to sample size [31]. A difference less than 0.1 was considered negligible.

The risk of IDH associated with ambient temperature was assessed using binary logistic regression. To account for the inter-correlations among HD sessions of the same patient, we applied the generalizing estimating equation (GEE) method with the first-order autoregressive (AR-1) as the working correlation matrix. The OR for risk of IDH per four degrees (around one SD) in temperature was presented, considering the SD of the pre-HD 24-hour mean ambient temperature was 4.4°C.

Sequential adjustments for covariates were made in the multivariable logistic regression models. We plotted the trend of crude and covariate-adjusted ORs of IDH per 2°C increase (0.5 SD of temperature) to
visualize the temperature-IDH relationship and determine if a threshold existed.

If a threshold was identified, we further fitted and tested the interaction term of “above and below the threshold” and “pre-HD 24-hour mean ambient temperature. A mediation analysis assessed the effects of temperature and UF/DW on IDH, adjusting for covariates. It used patient-specific random effects for repeated measures and Quasi-Bayesian confidence intervals from 1,000 bootstrap simulations. [32]

To assess if season may modify the effect of ambient temperature on IDH, we conducted a test for interaction between season and ambient temperature. Subsequently, subgroup analyses were conducted to assess the association of temperature with IDH by season. Seasons were categorized as Spring (March-May), Summer (June-August), Autumn (September-November), and Winter (December-February). Statistical analysis was conducted using SPSS and R. A \( p \)-value less than 0.05 was considered statistically significant.

RESULTS

Prevalence of IDH in Sessions by Multiple Definitions

We analyzed 110,400 HD sessions from 182 patients with 611,136 BP records. The prevalence of IDH in these sessions was estimated at 11.8% and 10.4% based on the reduction-based (Fall40) and nadir-based (Nadir90/100) criteria, respectively (Figure 2a and Table S2). The prevalence of IDH varied with ambient temperature, and the lowest and highest estimates were observed in hot (>31°C) and cold temperatures (<15°C) regardless of the IDH definition: 8.2% and 18% for Fall40 and 10.1% and 13.1% for Nadir90/100, respectively (Figure 2a).
**Characteristics of IDH Sessions**

The differences in session characteristics and medication use between sessions with IDH and without IDH are shown in Table 1. The characteristic with the greatest standardized difference was pre-HD SBP for both definitions. Interestingly, pre-HD SBP was higher in IDH sessions defined by the Fall40 criteria (155 in IDH vs. 134mmHg in non-IDH) but was lower (121 in IDH vs. 138mmHg in non-IDH) in IDH sessions determined by Nadir90/100. IDH sessions also tended to have higher ultrafiltration to dry weight ratio than non-IDH sessions for both criteria, 4.91% vs. 3.61% in Fall40 and 4.63% vs. 3.66% in Nadir90/100. Age and sex were also differently distributed between the definitions, with IDH sessions defined by Fall40 being younger and male, and IDH sessions defined by Nadir90/100 being older and female (Table 1).

**Relationship between Ambient Temperature and IDH**

We observed that the relationship between ambient temperature and IDH was not linear but exhibited a reverse J-shape pattern, indicating a possible inflection point around 27°C. The linear relationship was found only in temperatures below 27°C (Figure 3a and 3b). We performed a test for interaction and found significant results with p-values of 0.001 and 0.033 for both Fall40 and Nadir90/100 definitions, suggesting that the effect of temperature on the risk of IDH was significantly different between temperatures above and below 27°C (Table 2). However, using 26°C and 28°C as alternative cut-off points, the Nadir90/100 definition showed no consistent,
significant interaction. We then conducted stratified analyses. For
temperatures above 27°C, the ORs of IDH were 0.924 (95% CI 0.772 to 1.105)
for the Fall40 definition and 1.010 (95% CI 0.830 to 1.228) for the Nadir90/100
definition. In contrast, for temperatures below 27°C, the OR of IDH per
four-degree decrease was significantly increased at 1.292 (95% CI 1.228 to
1.358) and 1.207 (95% CI 1.149 to 1.268) for the Fall40 and Nadir90/100
definitions, respectively. Therefore, all subsequent analyses were limited to
temperatures <27°C.

**Temperature-IDH Relationship After Multivariable Adjustment**

In temperatures below the threshold of 27°C, we conducted univariate and
multivariable logistic regression analyses with adjustments for demographic
data, dialysis-related variables, and medications in models 1-3 accordingly
(Table 3). With IDH defined by Fall40, the crude and adjusted ORs were similar
across the univariate and adjusted models 1-3 with a change in OR <3%.
Conversely, the OR increased from 1.123 in the crude OR to 1.207 in the fully
adjusted OR, representing a 7% increase if IDH was defined by Nadir90/100.
The fully adjusted models showed that each 4°C decrease from 27°C to 6.2°C
was associated with an adjusted OR of 1.292 (95% CI 1.228 to 1.358) for
Fall40 and 1.207 (95% CI 1.149 to 1.268) for Nadir90/100.

**Causal mediation analysis**

Fluid removal (UF/DW) substantially mediated the effect of temperature on
intradialytic hypotension (IDH) risk, accounting for 23.16% (95% CI: 21.23% to
25.40%) of the total effect. (Table S4) Both direct and mediated effects were
Temperature Effect on IDH Across the Four Seasons

Analysis of interaction indicates that season significantly modifies the relationship between ambient temperature and IDH, according to the covariate-adjusted Nadir90/100 criteria (interaction p-value = 0.029). However, this interaction is not significant when assessed using the Fall40 criteria (interaction p-value = 0.728). After stratifying by four seasons, the low ambient temperature remained significantly associated with IDH in all seasons except summer. The adjusted ORs (95% CIs) of IDH defined by Fall40 were 1.267 (1.167 to 1.375), 0.863 (0.440 to 1.694), 1.368 (1.176 to 1.591), and 1.227 (1.136 to 1.325) in the spring, summer, autumn, and winter, respectively. The corresponding ORs for the Nadir90/100 definition were 1.251 (1.134 to 1.381), 0.886 (0.409 to 1.919), 1.207 (1.010 to 1.443), and 1.182 (1.093 to 1.277) (Table 4, Figure 3c and 3d).

Sensitivity Analysis

We conducted sensitivity analyses incorporating an additional five definitions outlined in Table S2. The temperature-IDH relationship based on these definitions revealed similar patterns (Figure S1). The characteristics of HD sessions according to various IDH definitions in sensitivity analysis are shown in Table S5. The threshold was evident in all definitions with $P_{\text{interaction}} < 0.05$ (Table S6). We repeated multivariable logistic regression and found the odds ratios to be similar in magnitude to those obtained using the Fall40 and Nadir90/100 definitions outlined in Table S7.
DISCUSSION

The current study found that low ambient temperature is associated with an increased risk of IDH. More specifically, for every 4°C drop in temperature, the odds ratio of IDH increased by 1.29 and 1.21 for the reduction-based and nadir-based definitions, respectively. Furthermore, our analysis revealed a statistically significant threshold of 27°C across all seven predetermined IDH definitions, with the reduction-based definition (Fall40) being particularly relevant for cold temperatures. Moreover, ambient temperature's impact on IDH was 23% mediated by changes in ultrafiltration (UF/DW). The relationship between temperature and IDH was consistent across all seasons except summer. These results have important implications for the management and care of hemodialysis patients, as well as for developing interventions and policies related to cold weather exposure.

In this study, we identified a threshold temperature of 27°C for the temperature-IDH relationship in southern Taiwan. An analysis of mortality in 11 Eastern US cities revealed that temperature was the most significant weather-related factor affecting mortality. Southern cities, which have similar latitudes to Taiwan, had a higher risk of mortality at lower temperatures, while lower risk at higher temperatures [33]. The study found threshold temperatures of 27.06°C and 27.18°C in Tampa and Miami, similar to a previously identified threshold of 27°C for cardiovascular mortality in Taiwan [6]. Although the threshold temperature associated with IDH risk may vary in different regions, the findings from our study might be generalized to regions with similar latitudes. Further studies across different regions and latitudes are needed.
The IDH definition is currently lacking consensus [13, 14, 34]. We used two primary definitions, both of which were reported to have a significant association with mortality in different patient populations. Shoji et al. [17] found that a reduction in systolic blood pressure SBP of more than 40mmHg (Fall40) was associated with 2-year mortality in a Japanese population. Flythe et al. [16] reported that Nadir90/100 was consistently associated with mortality in two large cohorts in the United States. Our analysis found Fall40 to be more strongly associated with cold temperatures. Cold temperatures are associated with high ultrafiltration (UF) rates, which are a risk factor for SBP decline and thus more likely to meet the criteria of Fall40. Besides, cold temperatures are linked to higher pre-HD SBP [35, 36], which may make individuals less likely to reach Nadir90/100 criteria, as the lowest intradialytic SBP determines it. Our results suggest that Fall40 is more sensitive to cold ambient temperatures. The potential impact of different definitions on the relationship between IDH and temperature should be further explored in future studies.

Previous research has shown that there are seasonal variations in hemodialysis initiation [37], reductions in intradialytic blood pressure [27], heart failure [38, 39], acute myocardial infarctions [40], and overall mortality [41], with the highest risks observed in winter. Our study differentiates between "winter" and "low temperatures" as they are related but not contextually identical. We conducted a stratified analysis to examine the difference in the temperature-IDH relationship in four seasons. The results indicate that cold temperature remained a risk factor for IDH across seasons in spring, autumn, and winter. This provided reassurance that certain season-related factors such as lifestyle, comorbidity, and diet would not confound the relationship obverted
in this study. In addition, such findings also challenged the perception that winter is the only season associated with an increased risk of IDH. (Table 4 and Figure 3d).

The analysis showed no significant association in the summer, possibly due to the hot and stable weather of southern Taiwan's summer, which has a small temperature variation with an interquartile range of around 2.1°C (Figure 2b). This lack of temperature variation may facilitate temperature acclimation, potentially reducing the risk of IDH [42-45]. Interestingly, the spring and autumn seasons had the highest adjusted odds ratios and most dispersed temperature distribution, aligning with the idea of temperature acclimation.

Our findings demonstrate a correlation between lower temperatures and increased IDH risk, with a negative relationship between temperature and ultrafiltration (UF/DW). (Figure S2) Mediation analysis found that approximately one-fourth of the IDH risk from cold temperature was attributable to increased ultrafiltration, suggesting that controlling ultrafiltration volumes may offer an opportunity to partially mitigate the influence of low temperatures on IDH. (Table S4) Besides, previous research has established the efficacy of indoor heating as a means of combating cold outdoor temperatures. One randomized controlled trial evaluated the effect of intensive room heating on blood pressure in healthy Japanese participants during the winter months [46]. The results showed that intensive heating was associated with a significant reduction in morning systolic blood pressure and a suppression of morning pressure surges compared to weak heating. However, further research is needed to ascertain the potential benefits of this intervention for dialysis patients.
Our study has several strengths. First, the large sample size of over 110,000 dialysis sessions improves the assessment of temperature exposure. The study matched each patient to temperature data from the nearest weather station. Second, we have collected detailed parameters of dialysis, such as ultrafiltration, dialysate temperature, dialysate calcium, and hemodialysis vintage, which are all important factors related to IDH. Adjustments for these parameters largely reduced the potential for confounding. Third, as most dialysis patients have hypertension, we adjusted for antihypertensive medications, which may significantly impact IDH. Fourth, we included living and deceased patients from our dialysis center, reducing the potential selection and survivorship bias. Lastly, the temporal relationship between temperature exposure and IDH is clear, as the temperature is traced back according to the timing of each session.

Despite all the efforts, this study has limitations. One limitation is that we could only investigate ambient temperature, not indoor temperature. However, a prior study found a strong correlation between outdoor and indoor temperatures when the outdoor temperature exceeded 12.7°C [47]. Moreover, when cold waves strike, the actual temperature patients are exposed to indoors may not be as cold as the recorded outdoor temperature, introducing potential exposure misclassification. This could potentially bias our results toward the null, however, the study still presents significant findings. While this study incorporates ultrafiltration normalized to dry weight (UF/DW), the inclusion of bioimpedance measurements would offer a more detailed representation of body fluid changes, which can be considered in future studies. Additionally, there may be confounding factors, such as patients’
adaptive behaviors to cold, that were not accounted for. However, we believe
that stratifying the data by season has partially controlled for these variables.
Another limitation is that this study was conducted in Tainan, Taiwan, a
subtropical climate city. Therefore, it's unclear if the findings apply to places
with different climates or latitudes. Further research is needed to assess the
generalizability of the findings.

CONCLUSION
Our study provides important insights into the relationship between low
ambient temperature and IDH. Low ambient temperature before hemodialysis
is associated with an increased risk of IDH regardless of IDH definitions.
Future studies should investigate the potential benefits of interventions such as
indoor heating for dialysis patients and the generalizability of these findings to
other latitudes and climates. In addition, clinicians should consider
environmental temperature a potential risk factor in patient care.
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AUTHORS’ CONTRIBUTIONS

K.H. Liu, J.M. Sung, Y.S. Tsai and C.Y. Li conceptualized and designed the study. T.S. Huang, P.C. Tsai, F.Y. Su, and J.H. Jiang performed data curation and GPS matching. J.H. Jiang provided supervision for data curation and matching process. K.H. Liu, B. Hsu conducted the main statistical analysis, assisted by P.C. Tsai, W.R. Lin and F.Y. Su. C.Y. Li, W.H. Chang, E.C.C. Lai, Y.S. Tsai advised on statistical aspects and interpretation of the data. K.H. Liu wrote the original draft of the manuscript. C.Y. Li, J.M. Sung, W.H. Chang, E.C.C. Lai and Y.H. Yang reviewed and edited the manuscript. All the authors...
participated in reviewing the manuscript and approved the final version to be published.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT

The data sharing is beyond the scope of the authorization from the patient's informed consent and from the Institutional Review Board.
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### Table 1. Characteristics of hemodialysis sessions according to IDH definitions.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total number</th>
<th>All sessions</th>
<th>Reduction-based (Fall40)</th>
<th>Nadir-based (Nadir90/100)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>non-IDH (n=97,397)</td>
<td>IDH (n=13,003)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-HD 24h. mean temp.(°C), mean (SD)</td>
<td>110,400</td>
<td>25.2(4.4)</td>
<td>25.3(4.3)</td>
<td>24.1(4.7)</td>
</tr>
<tr>
<td>Demographic data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr), mean (SD)</td>
<td>110,400</td>
<td>62.9(13.7)</td>
<td>62.9(13.7)</td>
<td>63.3(13.3)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>110,400</td>
<td>55,644(50.4)</td>
<td>47,837(49.1)</td>
<td>7,807(60.0)</td>
</tr>
<tr>
<td>DM, n (%)</td>
<td>110,400</td>
<td>48,180(43.6)</td>
<td>40,020(41.1)</td>
<td>8,160(62.8)</td>
</tr>
<tr>
<td>HTN, n (%)</td>
<td>110,400</td>
<td>83,010(75.2)</td>
<td>72,725(74.7)</td>
<td>10,285(79.1)</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>110,400</td>
<td>27,222(24.7)</td>
<td>24,380(25.0)</td>
<td>2,842(21.9)</td>
</tr>
<tr>
<td>CCI, mean (SD)</td>
<td>110,400</td>
<td>7.0(2.8)</td>
<td>7.0(2.9)</td>
<td>7.4(2.6)</td>
</tr>
<tr>
<td>Hemodialysis records</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD vintage (month), mean (SD)</td>
<td>110,400</td>
<td>59(53)</td>
<td>60(54)</td>
<td>52(46)</td>
</tr>
<tr>
<td>UF / DW (%), mean (SD)</td>
<td>108,635</td>
<td>3.76(1.80)</td>
<td>3.61(1.74)</td>
<td>4.91(1.85)</td>
</tr>
<tr>
<td>Pre-HD SBP (mmHg), mean (SD)</td>
<td>110,395</td>
<td>136(22)</td>
<td>134(21)</td>
<td>155(22)</td>
</tr>
<tr>
<td>Blood flow (ml/min), mean (SD)</td>
<td>110,084</td>
<td>275(36)</td>
<td>275(35)</td>
<td>277(38)</td>
</tr>
<tr>
<td>Dialysate flow (ml/min), mean (SD)</td>
<td>110,379</td>
<td>564(113)</td>
<td>560(110)</td>
<td>597(123)</td>
</tr>
<tr>
<td>Dialysate avg. temp.(°C), mean (SD)</td>
<td>110,231</td>
<td>36.1(0.4)</td>
<td>36.1(0.4)</td>
<td>36.0(0.4)</td>
</tr>
<tr>
<td>Conductivity (mEq/L), mean (SD)</td>
<td>109,769</td>
<td>140.0(0.6)</td>
<td>140.0(0.6)</td>
<td>140.0(0.7)</td>
</tr>
<tr>
<td>Dialysate calcium (mEq/L), n (%)</td>
<td>110,384</td>
<td>1,490(1.3)</td>
<td>1,336(1.4)</td>
<td>154(1.2)</td>
</tr>
<tr>
<td>1.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Antihypertensives and Iron use

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hb, mean (SD)</strong></td>
<td>110,374</td>
<td>10.6(1.0)</td>
<td>10.6(1.0)</td>
<td>10.6(1.0)</td>
<td>10.7(1.0)</td>
</tr>
<tr>
<td><strong>Antihypertensives and Iron use</strong></td>
<td>107,867</td>
<td>10.6(1.0)</td>
<td>10.6(1.0)</td>
<td>10.8(1.0)</td>
<td>10.7(1.0)</td>
</tr>
<tr>
<td>ACEi/ARB, n (%)</td>
<td>27,204(25.2)</td>
<td>24,320(25.0)</td>
<td>2,884(22.2)</td>
<td>26,216(26.5)</td>
<td>988(8.6)</td>
</tr>
<tr>
<td>Beta blockers, n (%)</td>
<td>31,692(29.4)</td>
<td>27,943(28.7)</td>
<td>3,749(28.8)</td>
<td>29,755(30.1)</td>
<td>1,937(16.9)</td>
</tr>
<tr>
<td>Alpha blockers, n (%)</td>
<td>11,912(11.0)</td>
<td>10,823(11.1)</td>
<td>1,089(8.4)</td>
<td>11,530(11.7)</td>
<td>382(3.3)</td>
</tr>
<tr>
<td>Calcium channel blocker, n (%)</td>
<td>40,708(37.7)</td>
<td>37,099(38.1)</td>
<td>3,609(27.8)</td>
<td>39,594(40.0)</td>
<td>1,114(9.7)</td>
</tr>
<tr>
<td>Vasodilator, n (%)</td>
<td>8712(8.1)</td>
<td>7951(8.2)</td>
<td>761(5.9)</td>
<td>8,289(8.4)</td>
<td>423(3.7)</td>
</tr>
<tr>
<td>IV_iron, n (%)</td>
<td>110,400</td>
<td>1,569(1.4)</td>
<td>1,392(1.4)</td>
<td>177(1.4)</td>
<td>1,457(1.5)</td>
</tr>
</tbody>
</table>

* Data presented as mean (SD) in the continuous variables, and numbers (n) with the percentage (%) in categorical variables. Temp., temperature; DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; HD, hemodialysis; UF/DW, ultrafiltration weight to dry weight ratio; SBP, systolic blood pressure; avg, average; Hb, hemoglobin; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; IV_iron, intravenous iron infusion. A standardized difference of < 0.1 was considered a negligible difference between groups.
Table 2. Logistic regression with GEE methods for risk of IDH per four degrees Celsius decrease above and below the threshold (27°C)

<table>
<thead>
<tr>
<th>Definition</th>
<th>Overall (n=105,895)</th>
<th>≤27°C (n=59,751)</th>
<th>&gt;27°C (n=46,144)</th>
<th>P_{interaction}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall (n=105,895)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall40</td>
<td>Adjusted OR</td>
<td>1.230</td>
<td>1.292</td>
<td>0.924</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>1.175-1.289</td>
<td>1.228-1.358</td>
<td>0.772-1.105</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.39</td>
</tr>
<tr>
<td>Nadir90/100</td>
<td>Adjusted OR</td>
<td>1.181</td>
<td>1.207</td>
<td>1.010</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>1.126-1.238</td>
<td>1.149-1.268</td>
<td>0.830-1.228</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.92</td>
</tr>
</tbody>
</table>

\(^a\) The number was reduced because of missing data.
\(^b\) Interaction for ambient temperature and temperature above/below the threshold 27°C.
\(^c\) Adjusted for age, sex, diabetes, coronary artery disease, CCI, HD vintage, ultrafiltration to dry weight ratio, pre-HD SBP, blood flow, dialysate flow, dialysate average temperature, conductivity, dialysate calcium, hemoglobin, antihypertensive medications and iron infusion.
<table>
<thead>
<tr>
<th>Definition</th>
<th>Univariate</th>
<th>Model 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Model 2&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Model 3&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall40</td>
<td>OR</td>
<td>1.244</td>
<td>1.257</td>
<td>1.273</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>1.186-1.305</td>
<td>1.197-1.319</td>
<td>1.210-1.338</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nadir90/100</td>
<td>OR</td>
<td>1.123</td>
<td>1.121</td>
<td>1.185</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>1.078-1.169</td>
<td>1.074-1.170</td>
<td>1.131-1.242</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup> Model 1 adjusted for age, sex, diabetes, hypertension, coronary artery disease, and Charlson Comorbidity Index.

<sup>b</sup> Model 2 adjusted for covariates in model 1 and additionally adjusted for HD vintage, ultrafiltration weight to dry weight ratio (UF/DW), pre-HD SBP, blood flow, dialysate flow, dialysate average temperature, conductivity, and dialysate calcium.

<sup>c</sup> Model 3 further adjusted for antihypertensive medications and iron infusion but omitted covariate of hypertension to avoid collinearity.
Table 4. Univariate and multivariable logistic regression for risk of IDH per four degrees Celsius decrease in four seasons (≤27°C)

<table>
<thead>
<tr>
<th>Definition</th>
<th>Unadjusted</th>
<th></th>
<th></th>
<th></th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Spring (n=18,781)</td>
<td>Summer (n=3,565)</td>
<td>Autumn (n=14,362)</td>
<td>Winter (n=25,526)</td>
<td>Spring (n=17,372)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Summer (n=3,271)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Autumn (n=13,383)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
<td></td>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
<td></td>
</tr>
<tr>
<td>Fall40</td>
<td>OR</td>
<td>1.278</td>
<td>1.260</td>
<td>1.415</td>
<td>1.189</td>
<td>1.267</td>
<td>0.863</td>
<td>1.368</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>1.196-1.366</td>
<td>0.753-2.108</td>
<td>1.232-1.625</td>
<td>1.119-1.264</td>
<td>1.167-1.375</td>
<td>0.440-1.694</td>
<td>1.176-1.591</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>&lt;0.001</td>
<td>0.38</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>P_interact</td>
<td></td>
<td>0.343</td>
<td></td>
<td></td>
<td></td>
<td>0.728</td>
<td></td>
</tr>
<tr>
<td>Nadir90/100</td>
<td>OR</td>
<td>1.136</td>
<td>0.884</td>
<td>1.158</td>
<td>1.110</td>
<td>1.251</td>
<td>0.886</td>
<td>1.207</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>1.050-1.229</td>
<td>0.510-1.533</td>
<td>1.006-1.333</td>
<td>1.047-1.177</td>
<td>1.134-1.381</td>
<td>0.409-1.919</td>
<td>1.010-1.443</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>0.002</td>
<td>0.66</td>
<td>0.041</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.76</td>
<td>0.038</td>
</tr>
<tr>
<td></td>
<td>P_interact</td>
<td></td>
<td>0.134</td>
<td></td>
<td></td>
<td></td>
<td>0.029</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Adjusted for age, sex, diabetes, coronary artery disease, Charlson Comorbidity Index, HD vintage, ultrafiltration to dry weight ratio, pre-HD SBP, blood flow, dialysate flow, dialysate average temperature, conductivity, dialysate calcium, hemoglobin, antihypertensive medications and iron infusion.

<sup>b</sup> The number is reduced because of missing data.

<sup>c</sup> Interaction for season and ambient temperature
Figure 1. (A) Patient enrollment and geographic information. Patient enrollment and prevalence of intradialytic hypotension (IDH), (B) Geographic information of southern Taiwan and the distance between the 21 weather stations of the Central Weather Bureau (blue marks) and the 182 home addresses assessed (red dots). Only 10 weather stations were shown in this figure due to the scale of figure. The dialysis center was marked as red mark. The figure was generated by Python 3.8.9 with the extension library, Folium 0.12.1.
Figure 2. Distribution of mean ambient temperature during all hemodialysis sessions, both with and without IDH (in a stacked bar chart, refer to the right vertical axis for session numbers) and the prevalence of IDH in specific temperatures (in a line chart, refer to the left vertical axis). (A) for the entire observation period from Jan 1, 2016 - Oct 31, 2021, or (B) broken down by four seasons.
Figure 3. Relationship between ambient temperature and risk of IDH compared with the subsets of highest temperature. (A) displays the crude odds ratio, while (B) shows the adjusted odds ratio with adjustments made for age, sex, diabetes, coronary artery disease, Charlson Comorbidity Index, ultrafiltration weight to dry weight ratio, pre-HD systolic blood pressure, blood flow, dialysate flow, dialysate mean temperature, conductivity, dialysate calcium, hemoglobin, and antihypertensive medication use. Additionally, the relationship between environmental temperature and the risk of IDH is further examined by season in (C) and (D), with crude and adjusted odds ratios, respectively, using the same adjustments as in (B).