Clinical Factors for Sudden Unexpected Death in Patients Undergoing Peritoneal Dialysis

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Abstract

Background: Sudden unexpected death (SUD) accounts for a significant proportion of overall mortality in patients undergoing peritoneal dialysis (PD). This study aimed to investigate the SUD clinical profiles in patients undergoing PD.

Methods: Medical records from January 2009 to December 2018 were retrospectively reviewed in a hospital-facilitated PD center in Taiwan. Demographic data, laboratory parameters, comorbidities, drug history, physical performance status, cardiac function parameters, and peritoneal transport category were abstracted. Cox proportional hazard regression was used to determine hazard ratio (HR) in SUD clinical profiles in patients undergoing PD.

Results: Based on 28 patients undergoing PD with SUD, 60 controls were matched for date of death on a 2:1 ratio for comparison. The incidence of diabetes and the prevalence of low physical performance status, analgesic drug use, concordant comorbidity number, mental health and chronic pain were higher in patients undergoing PD with SUD than in controls. In the cardiac function analysis, the QTc interval on the electrocardiogram was longer (467 vs. 453 ms, \( P=0.010 \)) in patients undergoing PD with SUD than in controls. At 3 months before death, patients who experienced SUD demonstrated progressive lower serum potassium concentrations. Cox proportional hazard regression analysis revealed that diabetes [adjusted HR, 4.73; 95% confidence interval (CI), 2.75–8.14; \( P<0.001 \)] and mental health and chronic pain (adjusted HR, 2.07; 95% CI, 1.06–4.05; \( P=0.033 \)) remain significant predictors for SUD in patients undergoing PD.

Conclusions: Diabetes mellitus, mental health and chronic pain, incidence of hypokalemia before death are significant clinical factors for SUD in patients undergoing PD.

Background

Patients undergoing dialysis are more predisposed to sudden death compared to the general population [1, 2]. Several speculated mechanisms have been proposed, including electrolyte abnormalities, acid–base imbalances, inappropriate ultrafiltration in dialysis sessions, intrinsic cardiac pathologies, inflammatory uremic milieu, autonomic nerve dysfunctions, presence of comorbidities, concomitant medications, and poor functional physical performance [1, 3–15]. Specifically, patients undergoing hemodialysis (HD) are more likely to suffer from sudden death than those undergoing peritoneal dialysis (PD) [1, 9, 14]. This result could be partly explained by the rapid changes in acid–base and electrolyte concentrations and plasma volume during intermittent HD sessions. In contrast, PD follows a gentler pattern to remove plasma volume and correct electrolyte and acid–base imbalance.

Recently, a few studies have performed survival analyses between HD and PD [1, 16–21]. Most of them focused on comparing the survival benefits in a defined period between HD and PD, with results presenting variable differences for survival benefits. Recently, a multicenter retrospective cohort study showed that differences in the incidence of sudden death were not significant between patients undergoing HD and PD [1]. A case-control study in one center showed that recent blood transfusion, male
sex, and diabetes mellitus increased the odds of sudden death in patients undergoing PD [22]. Moreover, investigators identified that other predictors were older age, ischemic heart disease, and decreased left ventricular ejection fraction (≤ 35%) [1]. However, whether additional clinical factors, e.g., demographic profile, trajectory electrolyte, and cardiac function changes, could be considered as potential factors for sudden death in patients undergoing PD remains unclear.

Thus, this study aimed to examine the relationship between clinical factors and SUD in patients undergoing PD. The identification of potential risk factors for SUD in patients undergoing PD was via a wide-range clinical data collection.

Methods

Subjects

This retrospective study was conducted to collect clinical information on prevalence in patients undergoing PD in Kaohsiung Chang Gung Memorial Hospital in Taiwan using data from January 2009 to December 2018. Patients undergoing maintenance PD for >3 months and experienced SUD during the study period were enrolled in this study. For the control selection, two controls were extracted from the dataset matched for date of one death during the study period by computer-generated block randomization method.

SUD Definition

SUD was defined as spontaneous death preceded by a sudden loss of consciousness within 1 h after the onset of acute symptoms, even in the presence of pre-existing heart disease, but with unexplained causes and unexpected timing and mode [23]. Confirmation of SUD was approved by medical professionals either in the hospital or the patients’ residence.

Informative data collection

Various clinical data were collected, including demographics, laboratory parameters, comorbidities, cardiac function measurements, drug history, and physical functional performance. Laboratory parameters were retrospectively collected continuously three months before SUD, including parameters of hemogram, biochemistry, and intact parathyroid hormone. Cardiac function measurements consisted of electrocardiogram (ECG) and echocardiography performed at the nearest time of SUD occurrence. PR, QRS, and QT interval values in ECG were collected. QTc interval was measured using an ECG machine with Bazett’s formula correction (QTc = QT/(RR)^{1/2}). Cardiac function was evaluated using Pulsed Doppler echocardiography. On the other hand, physical functional performance status was measured using the Karnofsky Performance Status scoring system [24].

Peritoneal equilibration test (PET)
Standard PETs were performed at 6-month intervals. The last values of PET-related parameters were collected before SUD. Glucose load was calculated using the peritoneal glucose load index (PGLI), referred to as the net glucose content in PD solutions in the daily PD dwell divided by the body weight (kg).

**Comorbidities**

Previously validated algorithms were used for comorbidities based on claims data [25]. Briefly, comorbidities were categorized into concordant, discordant, and mental health/chronic pain. Comorbidity status was determined for an individual patient within each fiscal year, using data in the fiscal year before the index data as baseline.

**Statistical analysis**

Baseline characteristics, cardiac function parameters, PET, and laboratory measurements of patients and controls were summarized as frequencies (percentage), means (standard deviation), or medians (interquartile range). For categorical variables, differences between patients and controls were estimated using chi-squared or Fisher’s exact test. For continuous variables, differences were estimated using the independent two-sample t-test. On the other hand, the difference of repeated laboratory measurements in each group was estimated using a one-way repeated analysis of variance (ANOVA) test, while a two-way repeated ANOVA was used for estimation of the difference of repeated laboratory measurements between patients and controls. Cox proportional hazard regression was used to determine the association between sudden death mortality and each included variable. The multivariate model included variables with \( p \)-values of <0.05 in the univariate analysis. \( p \)-values of <0.05 were considered statistically significant. All statistical analyses were performed with Stata version 14.0. (StataCorp, 2015; Stata Statistical Software: Release 14; College Station, TX, StataCorp, LP).

**Results**

**Patient Characteristics**

A total of 28 patients with SUD and 60 controls were included in the analyses. Patients with and without SUD had a mean age of 64 and 63 years, and 53.6% and 55.0% were women, respectively. Among the 28 patients with SUD, five (18%) were treated with automated PD and 23 (82%) underwent continuous ambulatory PD. Among the 60 controls, 21 (35%) were treated with automated PD, while 39 (65%) received continuous ambulatory PD. The proportions of lower Karnofsky scores (<80, 75% vs. 51.7%, \( P = 0.022 \)), no working capability (67.9% vs. 38.3%, \( P = 0.006 \)), diabetes (53.6% vs. 25.0%, \( P = 0.008 \)), and analgesic drug use (67.9% vs. 35%, \( P = 0.005 \)) were significantly higher in patients with SUD than in controls at baseline. On the other hand, patients with SUD significantly had more concordant comorbidities (\( P = 0.020 \)) and mental health and chronic pain (\( P = 0.001 \)) (Table 1).
| Variables                        | Case                  | Controls               | P       |
|---------------------------------|-----------------------|------------------------|---------|
| Case no. (row %)                | 28 (31.8%)            | 60 (68.2%)             |         |
| PD vintage (year )*             | 5.2 (3.4–7.1)         | 5.1 (4.4–7.3)          | 0.940   |
| Age (year)                      | 64.3 ± 12.8           | 63.2 ± 10.4            | 0.673   |
| Gender                          |                       |                        | 0.900   |
| Female                          | 15 (53.6%)            | 33 (55.0%)             |         |
| Male                            | 13 (46.4%)            | 27 (45.0%)             |         |
| Karnofsky score                 |                       |                        | 0.022   |
| 90–100                          | 6 (21.4%)             | 29 (48.3%)             |         |
| <=80                            | 21 (75%)              | 31 (51.7%)             |         |
| Working capability              |                       |                        | 0.006   |
| Yes                             | 8 (28.6%)             | 37 (61.7%)             |         |
| No                              | 19 (67.9%)            | 23 (38.3%)             |         |
| Main operator                   |                       |                        | 0.070   |
| Self                            | 15 (53.6%)            | 45 (75%)               |         |
| Others                          | 12 (42.9%)            | 15 (25%)               |         |
| Primary kidney disease          |                       |                        | 0.008   |
| Non-DM                          | 13 (46.4%)            | 45 (75.0%)             |         |
| DM                              | 15 (53.6%)            | 15 (25.0%)             |         |
| ARB/ACEI                        | 15 (53.6%)            | 32 (53.3%)             | 0.983   |
| CCB                             | 15 (53.6%)            | 34 (56.7%)             | 0.785   |
| Diuretic                        | 5 (17.9%)             | 8 (13.3%)              | 0.577   |
| β-Block                         | 12 (42.9%)            | 22 (36.7%)             | 0.619   |
| Analgesic drug                  | 19 (67.9%)            | 21 (35.0%)             | 0.005   |
| Antipsychotics                  | 17 (60.7%)            | 31 (51.7%)             | 0.427   |

Abbreviations: PD, peritoneal dialysis; DM, diabetes mellitus; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockade;

Data were expressed as mean ± SD, *, expressed as median (interquartile range).
### Variables

| Variables                     | Case          | Controls       | \( P \) |
|-------------------------------|---------------|----------------|--------|
| Comorbidities \( \triangle \) | \( \)        | 0.020          |        |
| Concordant no.                |               |                |        |
| 0                            | -             | 1 (1.7%)       |        |
| 1                            | 8 (28.6%)     | 31 (51.7%)     |        |
| 2                            | 12 (42.9%)    | 24 (40%)       |        |
| 3                            | 8 (28.6%)     | 4 (6.7%)       |        |
| Discordant no.                |               | 0.571          |        |
| 0                            | 11 (39.3%)    | 29 (48.3%)     |        |
| 1                            | 12 (42.9%)    | 24 (40%)       |        |
| 2                            | 5 (17.9%)     | 5 (8.3%)       |        |
| 4                            | -             | 1 (1.7%)       |        |
| Mental health and chronic pain| \( \)        | 0.001          |        |
| 0                            | 4 (14.3%)     | 26 (43.3%)     |        |
| 1                            | 13 (46.4%)    | 29 (48.3%)     |        |
| 2                            | 11 (39.3%)    | 5 (8.3%)       |        |

Abbreviations: PD, peritoneal dialysis; DM, diabetes mellitus; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockade; Data were expressed as mean \( \pm \) SD, *, expressed as median (interquartile range).

### Cardiac function measurements of the entire cohort

In the ECG analysis, patients with SUD had longer QTc interval at baseline compared with the controls (467 ms vs 453 ms, \( P = 0.01 \)). There were no significant differences in the left ventricular ejection fraction between SUD and controls (Table 2).
Table 2
Cardiac function measurements

| Cardiac function | Case          | Controls      | P     |
|------------------|---------------|---------------|-------|
| LVEF (%)         | 63.9 ± 8.7    | 65.6 ± 10.6   | 0.466 |
| EKG reading      |               |               |       |
| PR (ms)*         | 175 (157–209) | 173.7 (173–189) | 0.226 |
| QRS(ms)*         | 94 (84–104)   | 92.9 (91–100) | 0.114 |
| QTc(ms)*         | 467 (437–503) | 453 (449.5–473) | 0.010 |

Abbreviations: LVEF, left ventricular rejection fraction.; Data were expressed as mean ± SD, *-, expressed as median (interquartile range).

PET parameters

PET parameters, including peritoneal transport category, adequacy indices, residual creatinine clearance, and PGLI, were not significantly different between patients with SUD and controls (Table 3).
Table 3
Peritoneal equilibration test

| Variables          | Case     | Controls  | P     |
|--------------------|----------|-----------|-------|
| PET class          |          |           | 0.682 |
| Low, L (n, %)      | 2 (7.1%) | 3 (5.0%)  |       |
| Low average, LA (n, %) | 10 (35.7%) | 19 (31.7%) |       |
| High average, HA (n, %) | 14 (50%) | 31 (51.7%) |       |
| High, H (n, %)     | 1 (3.6%) | 7 (11.7%) |       |
| PGLI               | 2.51 ± 1.19 | 2.49 ± 1.15 | 0.590 |
| PET                |          |           |       |
| PD Kt/V            | 1.9 ± 0.4 | 1.7 ± 0.4 | 0.082 |
| Renal Kt/V         | 0.1 ± 0.3 | 0.2 ± 0.3 | 0.177 |
| Total Kt/V         | 2.0 ± 0.4 | 2.0 ± 0.3 | 0.539 |
| PD WCC             | 46.9 ± 7.6 | 43.0 ± 11.5 | 0.103 |
| Renal WCC          | 7.5 ± 17.5 | 12.6 ± 24.8 | 0.349 |
| Total WCC          | 57.1 ± 13.5 | 58.4 ± 22.0 | 0.778 |
| nPCR               | 1.0 ± 0.3 | 0.9 ± 0.2 | 0.357 |

Abbreviations: PET, peritoneal equilibration test; WCC, weekly creatinine clearance; PGLI, peritoneal glucose loading index; nPCR, normalized protein catabolic rate.

Longitudinal laboratory parameter changes at 3 months before SUD

Patients with SUD demonstrated significantly lower serum K levels at three months before death (4.1 to 4.0 to 3.63 mEq/L; \( P < 0.001 \)); however, these trend changes were not observed in controls. Considering between-group interactions and time, the difference in serum K trend changes was significant between patients with SUD and controls \( (P < 0.001) \) (Table 4).
Table 4
Repeated measurements three months before expired

| Variables | 3-month before | 2-month before | 1-month before | \( p^a \) | \( p^b \) |
|-----------|---------------|---------------|---------------|--------|--------|
| **Cases** |               |               |               |        |        |
| Alb (g/dL) | 3.36 ± 0.42   | 3.51 ± 1.42   | 3.30 ± 0.57   | 0.524  | 0.303  |
| Hb (g/dL)  | 9.89 ± 1.41   | 10.62 ± 3.90  | 9.80 ± 1.82   | 0.352  | 0.103  |
| Hct ( % )  | 29.86 ± 3.86  | 29.20 ± 6.41  | 29.28 ± 5.58  | 0.822  | 0.166  |
| Na (mEq/L) | 133 (131–134) | 133 (131–135) | 132.5 (130.5–136.5) | 0.931  | 0.619  |
| K (mEq/L)  | 4.1 ± 0.82    | 4.00 ± 0.69   | 3.63 ± 0.85   | 0.032  | <0.001 |
| Ca (mg/dL) | 9.58 ± 0.77   | 9.41 ± 0.73   | 9.36 ± 0.78   | 0.325  | 0.593  |
| P (mg/dL)  | 5.57 ± 1.59   | 5.73 ± 1.96   | 5.95 ± 1.86   | 0.587  | 0.718  |
| iPTH (pg/dL) | 206.8 (75–557) | 244.4 (92.1–581.8) | 259.8 (96.3–441.5) | 0.231  | -      |
| **Controls** |               |               |               |        |        |
| Alb (g/dL) | 3.59 ± 0.34   | 3.70 ± 0.37   | 3.69 ± 0.35   | 0.001  |        |
| Hb (g/dL)  | 9.70 ± 1.45   | 9.72 ± 1.49   | 9.85 ± 1.46   | 0.433  |        |
| Na (mEq/L) | 133 (131–136) | 135 (131–137) | 134 (132–136) | 0.409  |        |
| K (mEq/L)  | 3.87 ± 0.65   | 4.02 ± 0.57   | 4.09 ± 0.63   | 0.003  |        |
| Ca (mg/dL) | 9.51 ± 0.93   | 11.63 ± 15.82 | 9.50 ± 0.62   | 0.343  |        |
| P (mg/dL)  | 4.82 ± 1.05   | 4.85 ± 1.01   | 4.93 ± 1.12   | 0.486  |        |
| iPTH (pg/dL) | 221.1 (67.7–398.9) | -        | -             | -      | -      |

Abbreviations: Alb, albumin; Hb, hemoglobin; Na, sodium; K, potassium; Ca, calcium; P, phosphate; iPTH, intact parathyroid hormone, HCT, hematocrit;

\( p^a \) were estimated using one-way repeated ANOVA.

\( p^b \) were estimated using two-way repeated ANOVA, which is considering the interaction between groups and times.

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**Risk factors for SUD in patients undergoing PD**

Cox proportional hazard regression analysis revealed the following to be risk predictors for SUD: diabetes (crude hazard ratio [CHR], 6.01; 95% confidence interval [CI], 2.56–14.10; \( P < 0.001 \)), analgesic use (CHR, 2.26; 95% CI, 1.01–5.04; \( P = 0.047 \)), and mental health and chronic pain (CHR, 3.62; 95% CI, 1.64–7.99; \( P \))
= 0.001). After an adjusted analysis, diabetes (adjusted HR, 4.73; 95% CI, 2.75–8.14; \(P<0.001\)) and mental health and chronic pain (adjusted HR, 2.07; 95% CI, 1.06–4.05; \(P=0.033\)) remain as predictors for SUD in patients undergoing PD (Table 5).
| Variables                      | Comparison               | CHR (95% CI)       | P      | AHR (95% CI)     | P      |
|-------------------------------|--------------------------|--------------------|--------|------------------|--------|
| Age                           | years                    | 0.98 (0.94–1.01)   | 0.218  |                  |        |
| Gender, male                  | male vs female           | 1.12 (0.52–2.39)   | 0.777  |                  |        |
| Primary kidney disease        | DM vs Non-DM             | 6.01 (2.56–14.1)   | < 0.001| 4.73 (2.75–8.14) | < 0.001|
| Karnofsky score               | low vs high              | 1.74 (0.68–4.42)   | 0.245  |                  |        |
| Service ability               | No vs Yes                | 1.98 (0.85–4.61)   | 0.113  |                  |        |
| Main operator                 | others vs. self          | 1.81 (0.81–4.07)   | 0.148  |                  |        |
| PET class                     | HA/H vs LA/L             | 0.77 (0.35–1.67)   | 0.505  |                  |        |
| ARB/ACEI                      | yes vs no                | 0.78 (0.36–1.68)   | 0.521  |                  |        |
| CCB                           | yes vs no                | 0.99 (0.47–2.12)   | 0.988  |                  |        |
| Diuretic                      | yes vs no                | 1.96 (0.73–5.27)   | 0.180  |                  |        |
| β-Block                       | yes vs no                | 1.51 (0.69–3.32)   | 0.304  |                  |        |
| Analgesic drug                | yes vs no                | 2.26 (1.01–5.04)   | 0.047  | 1.03 (0.54–1.96) | 0.931  |
| Antipsychotics                | yes vs no                | 1.59 (0.71–3.57)   | 0.264  |                  |        |
| Concordant no.                | ≥ 2 vs 0–1               | 2.17 (0.93–5.03)   | 0.072  |                  |        |
| Discordant no.                | ≥ 2 vs 0–1               | 0.53 (0.16–1.80)   | 0.311  |                  |        |
| Mental health and chronic pain| ≥ 2 vs 0–1               | 3.62 (1.64–7.99)   | 0.001  | 2.07 (1.06–4.05) | 0.033  |
| PGLI                          | units                    | 0.96 (0.65–1.41)   | 0.819  |                  |        |
| PET                           |                          |                    |        |                  |        |
| Dialysis Kt/V                 | units                    | 0.70 (0.22–2.28)   | 0.558  |                  |        |
| RenalKt/V                     | units                    | 1.04 (0.19–5.81)   | 0.961  |                  |        |
| Total Kt/V                    | units                    | 0.64 (0.17–2.39)   | 0.511  |                  |        |
| Dialysis WCC                  | units                    | 1.01 (0.97–1.05)   | 0.568  |                  |        |
| Renal WCC                     | units                    | 1.01 (0.99–1.03)   | 0.420  |                  |        |

CHR: crude hazard ratio was estimated from univariate analysis. AHR: adjusted hazard ratio was estimated from multivariate analysis, variables with p-value less than 0.05 were included in multivariate analysis.
| Variables          | Comparison | CHR (95% CI)   |     | AHR (95% CI)   |     |
|-------------------|------------|----------------|-----|----------------|-----|
| Total WCC         | units      | 1.01 (0.98–1.03) | 0.743 |               |     |
| nPCR              | units      | 0.63 (0.11–3.46) | 0.594 |               |     |
| Cardiac function  |            |                |     |                |     |
| PR ms             |            | 1.01 (0.996–1.02) | 0.213 |               |     |
| QRS ms            |            | 1.01 (0.99–1.02)  | 0.467 |               |     |
| QTc ms            |            | 1.01 (0.999–1.01) | 0.075 |               |     |
| Laboratory        |            |                |     |                |     |
| measurements      |            |                |     |                |     |
| Albumin units (Time-dependent) |      | 1.11 (0.97–1.27)  | 0.124 | 0.91 (0.79–1.05) | 0.193 |
| Hb units (Time-dependent) |      | 0.99 (0.96–1.03)   | 0.690 | 1.03 (0.99–1.08) | 0.147 |
| Hct units (Time-dependent) |      | 0.99 (0.98–1.002)  | 0.107 | 0.99 (0.98–1.004) | 0.223 |
| Na units (Time-dependent) |      | 0.99 (0.97–1.002)  | 0.092 | 0.99 (0.97–1.01)  | 0.195 |
| K units (Time-dependent) |      | 0.99 (0.91–1.07)   | 0.761 | 1.04 (0.97–1.12) | 0.305 |
| Ca units (Time-dependent) |      | 1.06 (0.996–1.13)  | 0.065 | 0.99 (0.95–1.04)  | 0.736 |
| P units (Time-dependent) |      | 0.99 (0.96–1.03)   | 0.660 | 1.02 (0.99–1.05)  | 0.236 |
| iPTH units        |            | 0.9995 (0.998–1.001) | 0.396 |               |     |

CHR: crude hazard ratio was estimated from univariate analysis. AHR: adjusted hazard ratio was estimated from multivariate analysis, variables with p-value less than 0.05 were included in multivariate analysis.

**Discussion**

This study attempted to examine the clinical factors associated with SUD in patients undergoing PD. Using a long-term observational cohort, diabetes, K trajectory changes, and mental health and chronic pain were identified as risk factors for these patients. Given that majority of previous studies have focused on few parameters on sudden death in patients undergoing dialysis and rarely report on patients undergoing PD, more demographic data, clinical variables, and comorbidity discrimination were included.
in this study to examine their associations with SUD in patients undergoing PD. Our findings suggest that a multifaceted approach is potentially beneficial for SUD prevention in patients undergoing PD.

When examining the associations of SUD with demographics and comorbidities, patients with and without SUD were found to have similarities in age, sex, PD modalities, and antihypertensive drug use. Remarkably, patients with SUD had more concordant comorbidities at baseline compared with controls. These include some important cardiac comorbidities, e.g., hypertension, chronic heart failure and atrial fibrillation, diabetes, peripheral vascular disease, and stroke or transient ischemic attack [25]. All these comorbidities were observed in patients undergoing PD with SUD. In addition, majority of these patients demonstrated a prolonged QTc interval in this study. Given that previous studies reported that sudden cardiac death represents a major cause of mortality in patients with end-stage renal disease [1, 9, 11, 26], our results implicated that a planned schedule for cardiac function examination was essential for patients undergoing long-term dialysis.

To date, no studies have reported the association between mental health and chronic pain comorbidities and SUD in patients undergoing PD. We found that patients with SUD had more mental health and chronic pain comorbidities and were more likely to use analgesic drugs, mainly for chronic osteoarticular complaints. Furthermore, by hazard analysis, mental health and chronic pain comorbidities were identified as significant risk factors for SUD in patients undergoing PD. In our cohort, the proportion of patients undergoing PD with SUD who used analgesics was higher than that of controls, i.e., 67.9% and 35.0%, respectively. Analgesic categories included nonsteroidal anti-inflammatory drugs (NSAIDs) and a combination of NSAIDs with weak opioids. NSAIDs have been known to be associated with several adverse effects, including gastrointestinal and cardiac toxicity, blood pressure impairment, and renal toxicity [27]. These adverse effects may be related to fatal consequences [28]. Owing to unwitnessed SUD in some of our subjects, definitive causes of death could not be determined in our cohort. Nevertheless, an accumulating evidence has delivered a warning signaling the association between NSAIDs and fatal events in chronic kidney disease. Thus, we believe that an informative evaluation on the indication for NSAIDs in patients undergoing PD is mandatory to avoid SUD.

Diabetes has also been previously recognized as a risk factor for sudden death in the general population and patients undergoing dialysis especially in Asian population [6, 21, 29–31]. Proposed pathophysiology mechanisms for sudden death in diabetes include microvascular and macrovascular diseases. Among the causes of sudden death, sudden cardiac arrest is known as the primary mechanism [6, 29]. Diabetes triggers various untoward biological effects in the body. Consequently, pathologic changes appear in the organs and account for any observed functional impairment, especially in the heart. In this study, diabetes was a factor for SUD in patients undergoing PD. Our findings are consistent with these studies that showed diabetes led to a higher mortality rate in PD [21]. However, whether diabetic complication control could reduce the incidence of sudden death in diabetic patients undergoing dialysis remains to be elucidated.
Sudden cardiac arrest has been reported as the primary cause of sudden death in patients undergoing dialysis [4, 31]. Uremic milieu predisposes individuals with chronic kidney disease (CKD) to have cardiomyopathy and other vascular diseases [11]. These adverse effects consequently lead to arrhythmias, conduction abnormalities, and sudden cardiac arrest. One study investigated longitudinal changes in cardiac function and structure by echocardiography examinations in patients undergoing PD. The results showed the prevalence of altered cardiac structure and function upon PD initiation [32]. Patients undergoing dialysis are prone to sudden death through prolonged QTc interval or through increased arrhythmogenesis [11]. In this study, we found patients who were undergoing PD and experienced SUD showed longer QTc intervals compared to controls. Thus, patients undergoing dialysis are predisposed to cardiac structure and function abnormalities during the period of renal replacement therapy. Primary and secondary preventions of cardiac arrest could thus reduce SUD in patients undergoing dialysis.

Serum K pattern and its contribution to high cardiac risk has been reported in a large population of patients undergoing PD [33], wherein a U-shaped relationship between time-averaged serum K concentrations and cardiovascular mortality and all-cause mortality was found. The risk for all-cause mortality in cut-off serum K concentrations was < 3.5 mEq/L and ≥ 5.5 mEq/L, respectively [33]. Another smaller study showed that patients undergoing PD with lower time-averaged serum K concentrations and higher standard deviation had higher all-cause and cardiovascular mortality [34]. We found that patients who were undergoing PD and experienced SUD revealed progressively declining serum K concentrations at 3 months before SUD. Serum albumin concentrations also exhibited similar trends. However, synchronized data of ECG and plasma K concentrations were not obtained in our study. In addition, the definitive causes of hypokalemia in patients who were undergoing PD and experienced SUD also could not be obtained in this study. Considering serum K abnormalities, several spectra of cardiovascular diseases could be involved, including conduction defects, heart attack, and sudden cardiac death [35]. We propose that serum albumin and potassium trends in the last months could be a warning signal for SUD in patients undergoing PD.

The present study has notable limitations. First, information on the predictive performance for comorbidity on sudden death in patients undergoing dialysis is lacking. We used concordant and disconcordant variables for death prediction according to previous reports [25]. However, the tool needs to be validated further for consistent discrimination performance. Second, cardiac function and calcification scores were not comprehensively evaluated in this study. Therefore, the true influence of cardiac function on SUD in patients undergoing PD cannot be completely demonstrated in our study. Third, the sample size of SUD is relatively small, and to date, no universally accepted definition of SUD exists. Finally, this study was conducted retrospectively; therefore, anything reported in this study could be a hypothesis and prospective studies need to be conducted in the future.

Conclusions
In this study, we found that diabetes mellitus and mental health and chronic pain are significant predictors for SUD in patients undergoing PD. In addition, a trend for hypokalemia before death is significant in these patients. Given these results, a comprehensive framework has been attempted to design a therapeutic strategy to prevent SUD in prevalent patients undergoing PD.

**Abbreviations**

PD, peritoneal dialysis; HD, hemodialysis; SUD, sudden unexpected death; ECG, electrocardiogram; DM, diabetes mellitus; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockade; iPTH, intact parathyroid hormone; LV, Left ventricle; LVEF Left ventricular ejection fraction; PET, peritoneal equilibration test; RRF, residual renal function; WCC, weekly creatinine clearance; PGLI, peritoneal glucose loading index; nPCR, normalized protein catabolic rate; Alb, albumin; Hb, hemoglobin; Na, sodium; K, potassium; Ca, calcium; P, phosphate;

**Declarations**

The authors declared no conflict of interest.

**Ethics approval and consent to participate**

The Committee on Human Research at the Kaohsiung Chang Gung Memorial Hospital approved the data review protocol for this study (document no: 201800595B0). The requirement for patient consent was waived for medical chart review. The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Consent for Publication**

Not applicable.

**Availability of data and materials**

All data supporting the study is presented in the manuscript or available upon request from the corresponding author of this manuscript, Jin-Bor Chen.

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**Authors’ contributions**
Conceptualization, W.C.L. and J.B.C.; methodology, J.B.C.; validation, J.B.C., formal analysis, W.Y.Z., data curation, W.Y.Z. and T.W.H.; writing-original draft preparation, W.Y.Z.; writing-review and editing, W.X.C. and J.B.C.; supervision, C.H.W.; B.C.C..

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