Pre-Dialytic SpO2 Measured with a Wearable Device as a Predictor of Mortality in Patients with OSA and Chronic Kidney Disease

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Abstract: Hypoxemia and obstructive sleep apnea (OSA) have been recognized as a threat to life. Nonetheless, information regarding the association between pre-dialytic pulse oximeter saturation (SpO2) level, OSA and mortality risks remains mysterious in patients with maintenance hemodialysis (MHD). Bioclinical characteristics and laboratory features were recorded at baseline. Pre-dialytic SpO2 was detected using a novel microchip LED oximetry, and the Epworth Sleepiness Scale (ESS) score greater than 10 indicated OSA. Non-adjusted and adjusted hazard ratios (aHRs) of all-cause and cardiovascular (CV) mortality were analyzed for pre-dialytic SpO2, OSA and potential risk factors. During 2152.8 patient-months of follow-up, SpO2 was associated with incremental risks of all-cause and CV death (HR: 0.90 (95% CI: 0.82–0.98) and 0.88 (95% CI: 0.80–0.98), respectively). The association between OSA and CV mortality was significant (HR: 3.19 (95% CI: 1.19–9.38). In the multivariate regression analysis, pre-dialytic SpO2 still had an increase in all-cause and CV death risk (HR: 0.88 (95% CI: 0.79–0.98), 0.82 (95% CI: 0.71–0.96), respectively). Considering the high prevalence of silent hypoxia in the post COVID-19 era, a lower pre-dialytic SpO2 level and severe OSA warn clinicians to assess potential CV risks. In light of clinical accessibility, the microchip LED oximetry could be developed as a wearable device within smartphone technologies and used as a routine screen tool for patient safety in the medical system.

Keywords: pulse oximetry; obstructive sleep apnea; cardiovascular mortality; LED; wearable device; hemodialysis
1. Introduction

Hypoxemia is doomed to the common terminal pathway of multiple pathologies: clinicians are fearful of silent hypoxemia in the post COVID-19 era [1,2]. The intradialytic hypoxemia has been well recognized as a validated clinical predictor for inflammation, higher requirements of erythropoietin, and poor clinical outcomes [3–5]. Furthermore, coronary artery diseases (CAD) and obstructive sleep apnea (OSA) are closely related to hypoxia and are particularly common in patients with maintenance hemodialysis (MHD); it is no wonder that cardiovascular (CV) mortality remains the leading cause of death [3–6]. OSA is a disease that manifests with restriction of the airflow through the upper airways during sleep, leading to the development of hypertensive CV diseases, CAD, and cardiac arrhythmia [7]. Profound OSA patients are more prone to have apnea predominance, earlier arousals, rather shorter hypopnea duration, and significant desaturation, despite a similar apnea duration during sleeping [8]. Indeed, OSA is the most prevalent form of sleep-related breathing disorders, which is characterized by repetitive episodes of hypoxia, contributing to extremely high mortality rates, secondary to associated CV and metabolic risks [3].

In addition to conventional vital signs (body temperature, pulse rate, respiration rate, and blood pressure), studies have been increasing rapidly in the application of non-invasive screening systems to improve patient safety and predict clinical events in the high risk population [9]. Sudden cardiac death, intricately involved in heart rate variability, is highly prevalent among HD patients; there is, therefore, a need to develop a smart wearable device that has a microchip light emitting diodes (LED) sensor to detect pulse oximeter saturation (SpO2) [10–12]. In the post COVID-19 era, that has seen a high incidence of sudden death due to silent hypoxia, clinical assessments that reflect respiratory function would more likely relate to adverse outcomes, particularly in a burden of end-stage renal disease [1–3]. Given that OSA is a common chronic respiratory disorder resulting in raised morbidity and mortality, OSA characterized by frequent episodes of hypopneas, associated with intermittent hypoxemia, is now being recognized as a potential major risk factor of OSA-related death [13]. Despite previous documented information, the association between pre-dialytic SpO2 level, OSA and mortality risks needs be determined. Based on the above scenario, our hypothesis is to provide a combined evaluation of systemic oxygenation and underlying OSA severity for both all-cause and CV death. With respect to the clinical practicality and accessibility in a prognostic investigation, our research team used the Epworth Sleepiness Scale (ESS) score system for detecting severe OSA syndrome and our smart wearable LED oximetry device for pre-dialytic SpO2 in the MHD population-based study.

2. Materials and Methods

2.1. Cohort

Our study was approved by the Research Ethics Review Committee of En Chu Kong Hospital (ECKIRB1050402; ECKIRB1071203) based on the ethical standards of the committee and the Helsinki declaration for human research. Written informed consent was obtained from the participants of this study. The relevant details of the research methods were described previously [14]. Patients undergoing hemodialysis (HD) treatment for more than three months were eligible for inclusion. The definition of HD vintage was the duration of time between the first day of HD treatment and the first day that the patient entered this cohort. Each HD session of 3.5–4.5 h was performed with a blood flow rate of 200–300 mL/min and dialysate flow rate of 500 mL/min. We recorded blood pressure in the horizontal recumbent position before the dialysis session. Pre-dialytic blood samples were obtained from the existing vascular access. Research participants had to be older than 18 years of age and underwent regular HD, and 128 subjects fulfilled the enrollment rule. At the baseline, twenty-six participants were excluded from the study because they had inadequate dialysis, critical illness, sepsis, cancers, incomplete data or personal reasons. A total of ten patients were censored because they met one of the criteria listed below.
The following bioclinical characteristics and laboratory features of each participant were recorded at baseline: age, gender, hypertension, prior history of CAD, diabetes mellitus (DM), prevalent OSA, systolic and diastolic blood pressure, calcium, phosphorus, creatinine, potassium, pre-dialytic blood urea nitrogen, aspartate aminotransferase, blood glucose, albumin, uric acid, total cholesterol, triglyceride, iron profiles, hemoglobin, hematocrit, platelet count, HD vintage, SpO2 and OSA. The serum calcium was adjusted according to the following equation: adjusted calcium = measured calcium + ((4.0-serum albumin in g/dL) × 0.8). Standard procedures with certified methods were performed for all laboratory tests. The ESS questionnaire, with a total score of 10 or more, was utilized to screen severe OSA syndrome [15] (Supplementary Materials). Pre-dialytic levels of SpO2 were measured using a novel blood vessel analysis device, including a photoelectric detector, a processor, and an ultrasonic detector (US Patent 2018092631; Supplementary Data). The schematic diagram of our microchip LED array analysis was illustrated in Figure 1. Oxygen saturation values are between 95% and 100% for most healthy individuals according to the safety communication of the United States Food and Drug Administration (https://www.fda.gov/medical-devices/safety-communications/pulse-oximeter-accuracy-and-limitations-fda-safety-communication). Thus, SpO2 less than 95% was defined as abnormal blood-oxygen saturation, and normal pulse oximeter readings ranged from 95 to 100 percent [1,2,9].

Figure 1. The schematic diagram of the microchip LED array analysis. The blood vessel information comprises blood flow condition, oxygen content and heart rate variability. The application of specific integrated circuits in the microelectromechanical system is one of the revolutionary semiconductor components applied in the new era of medical system.

2.3. Outcome Measures

CV mortality of the current research was defined as death attributable to CAD, cardiac arrhythmia, heart failure, cardiac arrest because of other causes, ischemic stroke, intracerebral hemorrhage, pulmonary embolism, peripheral artery diseases and sudden, otherwise unexplained death [1,2,9]. The definition of non-CV mortality included all other causes of death, i.e., sepsis, cancers, gastrointestinal hemorrhage, traumatic events and miscellaneous. CV and non-CV death together referred to as all-cause mortality.
2.4. Statistics

Continuous variables were expressed as mean ± standard deviation, and categorical variables were presented as number (%). The univariable Cox model was applied to investigate the independence of risk factors associated with all-cause and CV mortality, including pre-dialytic SpO2, OSA, age, gender, DM, hypertension, prior CAD, total cholesterol, triglyceride, uric acid, blood urea nitrogen, creatinine, albumin, ferritin, hemoglobin, hematocrit, and platelet. The multivariable adjusted hazard ratios (aHRs) of mortality risks were analyzed for the independent risk factors generated from the unadjusted univariate Cox regression model. A p value < 0.05 was considered statistically significant. The SPSS version 22.0 (SPSS Inc. Chicago, IL, USA) was applied for data calculation in the current study.

3. Results

3.1. The Prevalence of Abnormal SpO2 Was 34.8% in the Study Population, and Approximately 10.9% of the Study Patients Had OSA

Finally, 92 MHD patients were included in our study sample with complete medical records and follow-up. The baseline bioclinical characteristics and laboratory features of the whole study population were demonstrated in Table 1. The mean age showed 62.8 ± 10.2 years; approximately 45% were male. The mean duration of follow-up was 23.4 ± 12.4 months. The mean body weight and BMI were 60.9 ± 9.9 kg and 23.9 ± 2.8 kg/m², respectively. The prevalence of DM, hypertension, OSA and CAD were 39.1%, 43.5%, 10.9% and 39.1%, respectively. According to the definition given by the United States Food and Drug Administration, the prevalence of abnormal pre-dialytic SpO2 was 34.8% in our observational study. The overall mortality rate was 25.0% during the 2152.8 patient-months of follow up. Among deceased patients, fifteen patients (65.2%) died from CV causes and the remaining eight (34.8%) were non-CV deaths.

Table 1. Baseline bioclinical characteristics and laboratory features of the whole study population.

| Variables                        | Overall (n = 92) |
|----------------------------------|-----------------|
| Age (years)                      | 62.8 ± 10.2     |
| Male, n (%)                      | 43 (44.2)       |
| Diabetes mellitus, n (%)         | 38 (41.3)       |
| Obstructive sleep apnea, n (%)   | 10 (10.9)       |
| Epworth Sleepiness Score         | 8.6 ± 1.7       |
| Hypertension, n (%)              | 40 (43.5)       |
| Prior coronary artery disease, n (%) | 36 (39.1) | 94.6 ± 3.3 |
| Pre-dialytic SpO2 (%)            | 32 (34.8)       |
| Abnormal SpO2, n (%)             | 32 (34.8)       |
| Body weight (kg)                 | 60.9 ± 9.9      |
| Body mass index (kg/m²)          | 23.9 ± 2.8      |
| Systolic blood pressure (mmHg)   | 139 ± 26        |
| Diastolic blood pressure (mmHg)  | 80 ± 17         |
| Hemodialysis vintage (months)    | 35.3 ± 23.2     |
| Aspartate aminotransferase (IU/L)| 16.6 ± 7.8      |
| Albumin (g/dL)                   | 3.9 ± 0.5       |
| Total cholesterol (mg/dL)        | 199.8 ± 53.6    |
| Triglyceride (mg/dL)             | 225.2 ± 184.1   |
| Blood urea nitrogen (mg/dL)      | 65.5 ± 16.0     |
| Creatinine (mg/dL)               | 10.3 ± 1.7      |
| Uric acid (mg/dL)                | 7.6 ± 1.4       |
| Potassium (mmol L⁻¹)             | 4.6 ± 0.8       |
| Adjusted calcium (mg/dL)         | 9.4 ± 0.8       |
| Phosphate (mg/dL)                | 4.6 ± 1.5       |
| Iron (µg/dL)                     | 78.5 ± 31.8     |
Table 1. Cont.

| Variables          | Overall (n = 92) |
|--------------------|-----------------|
| Ferritin (ng/mL)   | 612.1 ± 315.2   |
| Hemoglobin (g/dL)  | 10.7 ± 1.4      |
| Hematocrit (%)     | 32.0 ± 4.3      |
| Platelet (k/µL)    | 193.8 ± 64.1    |

Continuous variables were abbreviated as mean ± SD. Categorical variables are abbreviated as n (%). SpO2 = pulse oximeter saturation.

3.2. DM, Prior CAD History, OSA, and Pre-Dialytic SpO2 Values Differed Significantly between Event and Non-Event Groups According to All-Cause and CV Mortality

The prior CAD history, DM, prevalent OSA and pre-dialytic SpO2 values were significantly different between the death event and event-free groups according to all-cause mortality (Table 2).

Table 2. Comparisons of bio-clinical parameters between survivors and non-survivors according to all-cause mortality.

| Variables                                | Survivors (n = 69) | Deceased (n = 23) | p Value |
|------------------------------------------|--------------------|-------------------|---------|
| Age (years)                              | 62.6 ± 9.8         | 63.6 ± 11.5       | 0.684   |
| Male, n (%)                              | 32 (46.4)          | 11 (47.8)         | 0.905   |
| Diabetes mellitus, n (%)                 | 23 (33.3)          | 15 (65.2)         | <0.01   |
| Obstructive sleep apnea, n (%)           | 4 (5.8)            | 6 (26.1)          | <0.05   |
| Hypertension, n (%)                      | 27 (39.1)          | 13 (56.5)         | 0.148   |
| Prior coronary artery disease, n (%)     | 23 (33.3)          | 13 (56.5)         | <0.05   |
| Pre-dialytic SpO2 (%)                    | 95.2 ± 2.2         | 93.0 ± 5.0        | <0.05   |
| Body weight (kg)                         | 61.3 ± 10.1        | 59.6 ± 9.2        | 0.482   |
| Body mass index (kg/m²)                  | 24.0 ± 2.8         | 23.5 ± 2.8        | 0.549   |
| Systolic blood pressure (mmHg)           | 136 ± 23           | 148 ± 32          | 0.063   |
| Diastolic blood pressure (mmHg)          | 78 ± 14            | 85 ± 24           | 0.056   |
| Aspartate aminotransferase (IU/L)        | 16.4 ± 7.4         | 17.4 ± 9.1        | 0.597   |
| Albumin (g/dL)                           | 3.9 ± 0.5          | 3.8 ± 0.4         | 0.508   |
| Total cholesterol (mg/dL)                | 192.3 ± 52.8       | 212.3 ± 45.0      | 0.110   |
| Triglyceride (mg/dL)                     | 182.4 ± 137.0      | 207.4 ± 107.0     | 0.429   |
| Blood urea nitrogen (mg/dL)              | 66.1 ± 15.7        | 63.8 ± 17.1       | 0.556   |
| Creatinine (mg/dL)                       | 10.1 ± 1.7         | 10.7 ± 1.5        | 0.210   |
| Uric acid (mg/dL)                        | 7.5 ± 1.4          | 7.7 ± 1.5         | 0.624   |
| Potassium (mmol L⁻¹)                     | 4.6 ± 0.9          | 4.4 ± 0.8         | 0.371   |
| Adjusted calcium (mg/dL)                 | 9.4 ± 0.8          | 9.2 ± 0.8         | 0.185   |
| Phosphate (mg/dL)                        | 4.6 ± 1.6          | 4.7 ± 1.2         | 0.699   |
| Iron (µg/dL)                             | 79.7 ± 34.3        | 75.0 ± 23.7       | 0.549   |
| Ferritin (ng/mL)                         | 596.1 ± 285.0      | 657.4 ± 392.2     | 0.426   |
| Hemoglobin (g/dL)                        | 10.8 ± 1.4         | 10.2 ± 1.4        | 0.116   |
| Hematocrit (%)                           | 32.4 ± 4.3         | 31.0 ± 4.3        | 0.166   |
| Platelet (k/µL)                          | 195.3 ± 67.1       | 189.2 ± 55.3      | 0.694   |

Continuous variables were abbreviated as mean ± SD. Categorical variables are abbreviated as n (%). SpO2 = pulse oximeter saturation.

Specifically, the comparison between survivors and non-survivors demonstrated prior CAD history (33.3 vs. 56.5%; p-value < 0.05), DM (33.3 vs. 65.2%; p-value < 0.01); OSA (5.8 vs. 26.1%; p-value < 0.05); and pre-dialytic SpO2 value (95.2 ± 2.2% vs. 93.0 ± 5.0%; p-value < 0.05), respectively. Compared with the non-event group, the event group of all-cause mortality had higher prevalence of hypertension and the mean systolic and diastolic blood pressure (27 (39.1%) vs. 13 (56.5%); 136 ± 23 vs. 148 ± 32 mmHg; 78 ± 14 vs. 85 ± 24 mmHg, respectively). However, the p-value was insignificant (0.148; 0.063; 0.056, respectively). Likewise, the event group compared with the event-free group favored higher circulating levels of total cholesterol (212.3 ± 45.0 vs. 192.3 ± 52.8 mg/dL), lower levels of serum albumin (3.8 ± 0.4 vs. 3.9 ± 0.5 g/dL, p = 0.508), hemoglobin (10.2 ± 1.4 vs. 10.8 ± 1.4 g/dL, p = 0.116) and hematocrit (31.0 ± 4.3 vs. 32.4 ± 4.3%, respectively).
The similar results were found in the comparison between CV event and non-CV event groups according to CV mortality (Table 3). In summary, DM, prior CAD history, OSA, and pre-dialytic SpO2 values differed significantly between event and non-event groups with respect to all-cause and CV mortality.

Table 3. The comparison bio-clinical parameters between non-CV event group and CV event group according to CV mortality.

| Variables                        | Non-CV Event Group (n = 77) | CV Event Group (n = 15) | p Value |
|----------------------------------|-------------------------------|-------------------------|---------|
| Age (years)                      | 62.8 ± 9.9                   | 63.2 ± 12.1             | 0.893   |
| Male, n (%)                      | 35 (45.5)                    | 8 (53.3)                | 0.581   |
| Diabetes mellitus, n (%)         | 26 (33.8)                    | 10 (66.7)               | <0.05   |
| Obstructive sleep apnea, n (%)   | 5 (6.5)                      | 5 (33.3)                | <0.05   |
| Hypertension, n (%)              | 32 (41.6)                    | 8 (53.3)                | 0.406   |
| Prior coronary artery disease, n (%) | 25 (32.5)                    | 11 (73.3)               | <0.05   |
| Pre-dialytic SpO2 (%)            | 95.0 ± 2.4                   | 92.7 ± 5.7              | <0.05   |
| Body weight (kg)                 | 61.0 ± 9.9                   | 60.2 ± 9.8              | 0.762   |
| Body mass index (kg/m²)          | 24.0 ± 2.8                   | 23.4 ± 2.9              | 0.489   |
| Systolic blood pressure (mmHg)   | 138 ± 25                     | 146 ± 31                | 0.288   |
| Diastolic blood pressure (mmHg)  | 79 ± 15                      | 83 ± 25                 | 0.371   |
| Aspartate aminotransferase (IU/L)| 16.6 ± 8.2                   | 16.9 ± 5.7              | 0.903   |
| Albumin (g/dL)                   | 3.9 ± 0.5                    | 3.7 ± 0.4               | 0.066   |
| Total cholesterol (mg/dL)        | 197.4 ± 53.9                 | 211.5 ± 52.5            | 0.356   |
| Triglyceride (mg/dL)             | 227.3 ± 200.0                | 214.9 ± 70.0            | 0.677   |
| Blood urea nitrogen (mg/dL)      | 65.6 ± 15.4                  | 65.1 ± 20.6             | 0.918   |
| Creatinine (mg/dL)               | 10.2 ± 1.7                   | 10.7 ± 1.4              | 0.264   |
| Uric acid (mg/dL)                | 7.5 ± 1.3                    | 7.9 ± 1.7               | 0.395   |
| Potassium (mmol/L⁻¹)             | 4.6 ± 0.9                    | 4.4 ± 0.7               | 0.469   |
| Adjusted calcium (mg/dL)         | 9.4 ± 0.8                    | 9.2 ± 0.9               | 0.294   |
| Phosphate (mg/dL)                | 4.6 ± 1.6                    | 4.8 ± 1.0               | 0.606   |
| Iron (µg/dL)                     | 81.1 ± 33.7                  | 66.0 ± 15.6             | 0.093   |
| Ferritin (ng/mL)                 | 603.5 ± 306.7                | 654.2 ± 362.5           | 0.573   |
| Hemoglobin (g/dL)                | 10.7 ± 1.5                   | 10.6 ± 1.2              | 0.805   |
| Hematocrit (%)                   | 32.0 ± 4.4                   | 32.0 ± 3.6              | 0.932   |
| Platelet (k/µL)                  | 192.6 ± 66.9                 | 200.0 ± 48.2            | 0.683   |

Continuous variables were abbreviated as mean ± SD. Categorical variables are abbreviated as n (%). SpO2 = pulse oximeter saturation.

3.3. The Lower Pre-Dialytic Level of SPO2 and OSA Group Were Associated with an Incremental Risk for All-Cause and CV Mortality

Table 4 summarized the results in the univariate Cox regression analysis for potential prognostic factors with respective to all-cause and CV mortality.

A history of DM, lower pre-dialytic levels of SPO2, lower serum concentrations of albumin, and lower levels of hemoglobin were significantly associated with all-cause mortality (all p values < 0.05). Furthermore, prior history of CAD, DM, lower pre-dialytic levels of SPO2, prevalent OSA and lower serum concentrations of albumin were significantly associated with CV mortality (all p values < 0.05). However, the prevalent OSA was associated with CV mortality rather than all-cause death. In light of the significant results in the univariate Cox regression analysis for CV mortality, the above clinical risk factors of CAD, DM, lower pre-dialytic levels of SPO2, prevalent OSA and albumin concentrations were included in the multivariate Cox regression model. After multivariate adjustment, our data demonstrated that a lower pre-dialytic level of SPO2 was still significantly associated with incremental risks in all-cause mortality (Table 5).

Figure 2 illustrated the cumulative event-free survival curves of CV mortality with respect to normal and abnormal groups of pre-dialytic SpO2 divided by 95% after multivariate adjustment in the Cox regression model. The multivariable-adjusted results demonstrated the association between the abnormal pre-dialytic level of SPO2, and CV mortality remained robust (aHR: 0.296 (95% CI: 0.090–0.979); p values = 0.046).
Table 4. The univariate Cox regression model for all-cause and CV mortality with respect to various prognostic factors.

|                | All-Cause Mortality | CV Mortality |
|----------------|---------------------|--------------|
|                | HR (95% CI)         | p-Value      | HR (95% CI) | p-Value |
| SpO2           | 0.895 (0.821–0.975) | p < 0.05     | 0.884 (0.799–0.978) | p < 0.05 |
| Age            | 1.041 (0.996–1.088) | p = 0.075    | 1.0361 (0.981–1.095) | p = 0.200 |
| DM             | 2.518 (1.067–5.942) | p < 0.05     | 3.691 (1.118–11.600) | p = 0.05  |
| CAD            | 1.792 (0.780–4.068) | p = 0.170    | 3.766 (1.198–11.844) | p < 0.05  |
| Hypertension   | 1.083 (0.474–2.471) | p = 0.850    | 1.443 (0.523–3.983) | p = 0.479 |
| OSA            | 2.249 (0.883–5.726) | p = 0.089    | 3.190 (1.085–9.382) | p < 0.05  |
| Cholesterol    | 1.001 (0.993–1.009) | p = 0.766    | 1.001 (0.991–1.011) | p = 0.865 |
| Triglyceride   | 1.001 (0.998–1.004) | p = 0.683    | 1.002 (0.999–1.005) | p = 0.250 |
| Uric acid      | 1.074 (0.819–1.407) | p = 0.606    | 1.170 (0.866–1.581) | p = 0.307 |
| BUN            | 1.000 (0.974–1.026) | p = 0.971    | 1.005 (0.974–1.037) | p = 0.764 |
| Creatinine     | 1.114 (0.851–1.458) | p = 0.431    | 1.146 (0.818–1.607) | p = 0.428 |
| Albumin        | 0.271 (0.090–0.814) | p < 0.05     | 0.116 (0.033–0.414) | p < 0.05  |
| Ferritin       | 1.001 (0.999–1.003) | p = 0.184    | 1.001 (0.999–1.003) | p = 0.293 |
| Hemoglobin     | 0.739 (0.548–0.998) | p < 0.05     | 0.888 (0.593–1.330) | p = 0.564 |
| Hematocrit     | 0.913 (0.823–1.013) | p = 0.087    | 0.977 (0.849–1.125) | p = 0.750 |
| Platelet       | 0.996 (0.990–1.003) | p = 0.262    | 0.999 (0.991–1.007) | p = 0.775 |

Table 5. Multivariable Cox regression model for all-cause and CV mortality with respect to potential prognostic factors.

|                | All-Cause Mortality | CV Mortality |
|----------------|---------------------|--------------|
|                | HR (95% CI)         | p-Value      | HR (95% CI) | p-Value |
| SpO2           | 0.880 (0.792–0.977) | p < 0.05     | 0.823 (0.710–0.955) | p < 0.05 |
| OSA            | 1.082 (0.306–3.818) | p = 0.903    | 0.701 (0.128–3.631) | p = 0.682 |
| DM             | 1.994 (0.761–5.177) | p = 0.161    | 3.225 (0.801–12.985) | p = 0.099 |
| CAD            | 1.347 (0.533–3.405) | p = 0.529    | 3.001 (0.832–10.830) | p = 0.093 |
| Albumin        | 0.337 (0.088–1.282) | p = 0.110    | 0.118 (0.018–0.768) | p < 0.05  |

Boldface indicates where the values differ significantly between event-free survivors and non-survivors. CAD = coronary artery disease; BUN = blood urea nitrogen; OSA = obstructive sleep apnea; SpO2 = pulse oximeter saturation; HR = hazard ratio; CI = confidence interval.

**Figure 2.** Cumulative event-free survival curves of cardiovascular mortality with respect to pre-dialytic SpO2 after adjusting for OSA, albumin, diabetes, and prior history of CAD during 2152.8 patient-months of follow up. The green line indicates MHD patients with abnormal levels of SpO2 (<95%), and the green line indicates MHD patients with normal levels of SpO2 (95–100%). CAD = coronary artery disease; OSA = obstructive sleep apnea; SpO2 = pulse oximeter saturation.
4. Discussion

In the present study, our data showed that the prevalence of abnormal SpO2 was 34.8% in the MHD population, and approximately 10.9% of the study patients had an ESS score of more than 10 (Table 1). As expected, the CV mortality rate (65.2%) was much higher than non-CV deaths (34.8%) in our MHD cohort during follow-up (Table 2). The CV-event group had, indeed, a higher prevalence of prior CAD history, DM, OSA and pre-dialytic SpO2 value, respectively (all \( p \)-values < 0.05) (Table 3). In the univariate Cox regression model for all-cause mortality, our results demonstrated MHD patients with DM history and lower pre-dialytic levels of SpO2 had greater risks for all-cause death [HR: 0.895 (95% CI: 0.821–0.975), \( p \)-values < 0.05; 2.518 (95% CI: 1.067–5.942), \( p \)-values < 0.05; respectively] (Table 4). Furthermore, DM, CAD, OSA, and lower levels of pre-dialytic SpO2 had greater risks for CV death (all \( p \)-values < 0.05). After adjusting above significant risk factors in the multivariable Cox regression model, our results demonstrated MHD patients with DM history and lower pre-dialytic SpO2 had greater risks for CV death (all \( p \)-values < 0.05) (Figure 2).

Hypoxemia during hemodialysis has been well-studied in the past years, and several mechanistic explanations have been proposed. Intradialytic hypoxemia has been observed in patients while sleeping during the session of HD [4]. Because CO2 may diffuse from the blood into the dialysate, a decrease in respiratory drive has been incriminated, leading to reduced partial pressure of CO2 and the pH in the blood. Given that breathing is tightly controlled by chemoreceptors correlated with the levels of CO2 and pH in the blood and cerebrospinal fluid, a reduction in circulating CO2 partial pressure may result in hypoventilation and hypoxemia [4]. Fluid overload, lung edema, heart failure and CAD-induced pulmonary congestion may affect oxygen diffusion, resulting in reduced blood oxygenation. Accordingly, the therapeutic strategy of approaching dry weight could improve systemic oxygenation. Nonetheless, monitoring the intradialytic change of blood oxygenation may be too late. To deploy a timely and effective therapeutic strategy in preparation, a robust screening tool to warn clinicians in advance is crucial for the MHD population. To avoid intradialytic events, pre-dialytic SpO2 measurement serves as an optimal medical parameter to improve patient safety and deliver early detection for high-risk subjects in the post COVID-19 era.

Why should we pay more attention to hypoxia in the post COVID-19 era? The angiotensin-converting enzyme 2 (ACE2) is SARS-CoV-2 receptor of the cell, which is expressed in the carotid body, the chemoreceptors to sense oxygen [1]. Meanwhile, ACE2 receptors are distributed in nasal mucosa. A total of two thirds of patients with COVID-19 suffer from anosmia-hyposmia [18]. Furthermore, the olfactory bulb accounts for a passage along which certain Coronavirus enter the central nervous system [19]. Emerging evidence indicates a link between silent hypoxemia and the thrombi formation within the CV system and pulmonary vasculature [20]. Increased thrombogenesis and vascular inflammation could lead to severe hypoxemia and subsequent CAD and CV deaths in various populations [5,14,21–23]. A recent study specifically states that the lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) and the potent vasoconstrictor endothelin-1 (ET-1) are intricately involved in atherosclerotic plaques formation and assisting in detecting the CV risk in OSA subjects, respectively [24]. Indeed, there is a growing body of research that links OSA to arrhythmias and sudden cardiac death [25]. Intriguingly, a bidirectional relationship interplays between chronic kidney disease and OSA; and vice versa, continuous, supplemental oxygen therapy with continuous, positive airway pressure improves the renal function in OSA patients [16]. To investigate it further, we conducted the current study. Several limitations were found in the study. To begin with, the cross-sectional
laboratory values could not reflect substantial intra-individual variability over time. Second, our patients were predominantly an Asian study sample, limiting generalization to other populations. Moreover, ESS is a screening tool for daily sleepiness, which is usually followed by polysomnography in case the scores are above the mentioned thresholds. The polysomnography remains the gold standard for the diagnosis of OSA. Finally, prospective nonrandomized analysis might be subject to residual confounders.

5. Conclusions

With respect to the extremely high rate of sudden cardiac death in the MHD population, a comprehensive healthcare system for early detection of high-risk subjects is of prime importance. In the post COVID-19 era, which has seen a high prevalence of silent hypoxia, a lower pre-dialytic SpO2 level and severe OSA warn clinicians to assess for potential CV risks and determine a prompt and appropriate management. Relying on clinical accessibility, the microchip LED oximetry could be developed as a wearable device and used as a routine screen tool for patient safety in the medical system.

6. Patients

The study was approved by the Research Ethics Review Committee of En Chu Kong Hospital (ECKIRB1050402; ECKIRB1071203) in accordance with the ethical standards of the committee and the Helsinki declaration for research in humans. The relevant details of the research methods were described previously [14]. Patients undergoing MHD treatment for at least three months were eligible for enrollment. All patients had to be older than 18 years of age and receive thrice-weekly hemodialysis, and 92 MHD patients, willing to participate in the study, were included. Patients were censored if they met one of the criteria listed below during the follow-up: (1) patients were transferred to another dialysis unit; (2) patients abandoned HD treatment; (3) patients switched to peritoneal dialysis; (4) patients lost to follow up; and (5) patients received the renal transplant.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/app112210674/s1, ESS questionnaire.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The numeric data used to support the findings of this study are available from the corresponding author, J.-F.C. and J.-C.L., upon reasonable request. Corresponding author’s email: 01508@km.eck.org.tw; jcliou@tmu.edu.tw.

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