






Article

# Oxygen Extraction and Mortality in Patients Undergoing Chronic Haemodialysis Treatment: A Multicentre Study

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**Abstract:** Patients on haemodialysis (HD) suffer a high mortality rate linked to developing subclinical hypoxic parenchymal stress during HD sessions. The oxygen extraction ratio (OER), an estimate of the oxygen claimed by peripheral tissues, might represent a new prognostic factor in HD patients. This study evaluated whether the intradialytic change in OER ( $\Delta$ OER) identified patients with higher mortality risks. We enrolled chronic HD patients with permanent central venous catheters with available central venous oxygen saturation (ScvO<sub>2</sub>) measurements; the arterial oxygen saturation was measured with peripheral oximeters (SpO<sub>2</sub>). We measured OER before and after HD at enrolment; deaths were recorded during two-years of follow-up. In 101 patients (age:  $72.9 \pm 13.6$  years, HD vintage:  $9.6 \pm 16.6$  years), 44 deaths were recorded during  $11.6 \pm 7.5$  months of follow-up. Patients were divided into two groups according to a 40%  $\Delta$ OER threshold ( $\Delta$ OER < 40%, n = 56;  $\Delta$ OER  $\geq$  40%, n = 45). The  $\Delta$ OER  $\geq$  40% group showed a higher incidence of death (60% vs. 30%;  $p = 0.005$ ). The survival curve (log-rank-test:  $p = 0.0001$ ) and multivariate analysis ( $p = 0.0002$ ) confirmed a  $\Delta$ OER  $\geq$  40% as a mortality risk factor. This study showed the intradialytic  $\Delta$ OER  $\geq$  40% was a mortality risk factor able to highlight critical hypoxic damage. Using a  $\Delta$ OER  $\geq$  40% could be clinically applicable to characterise the most fragile patients.

**Keywords:** haemodialysis; oxygen extraction; end-stage renal disease; subclinical parenchymal hypoxia; central venous catheter; mortality; central venous oxygen saturation



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## 1. Introduction

Patients with end-stage renal disease (ESRD) undergoing chronic haemodialysis (HD) therapy have an increased risk of mortality secondary to the high prevalence of classical cardiovascular risk factors, the presence of risk factors characteristic of chronic kidney disease [1], and nonphysiological HD treatments [2]. HD treatment involves rapid changes in the blood volume and electrolytes, which can result in transient but repeated alterations of organ functions [3]. These alterations are attributable to the need for some parenchyma to increase their metabolic activity during the HD session, with an increase in O<sub>2</sub> consumption. However, this is associated with a reduced availability of O<sub>2</sub> linked to the relative hypovolaemia secondary to the rate of ultrafiltration and dialysis-related changes. In particular, alkalization of the peripheral blood and a reduction of the erythrocyte diphosphoglycerol concentration modify the dissociation curve of haemoglobin, increasing its affinity for O<sub>2</sub>, with a consequent reduction in the O<sub>2</sub> delivery from haemoglobin to the parenchyma [4,5]. Therefore, regardless of the development of symptoms, an imbalance between O<sub>2</sub> demand

and availability during the HD session results in subclinical parenchymal hypoxia, which causes acute organ function changes, such as myocardial stunning and reduced cerebral perfusion, that are related to long-term organ damage [6,7] and mortality [8]. Accordingly, a parameter able to show and estimate parenchymal hypoxia during HD might be very useful for identifying patients who develop greater intradialytic fatigue, which results in a greater clinical risk. Recently, the oxygen extraction ratio (OER), i.e., the ratio between the arterial oxygen saturation (SaO<sub>2</sub>) and central venous oxygen saturation (ScvO<sub>2</sub>), has been proposed as a monitoring system to underline the development of intradialytic subclinical parenchymal hypoxia in HD patients with a central venous catheter since this measurement is only possible in patients with CVC. In any case, the percentage of patients requiring this type of vascular access for long term haemodialysis treatment is increasing, reaching an average prevalence rate of 60% in a recent retrospective study [9]. Two monocentric studies have shown that the OER increases rapidly during HD sessions and that the extent of its intradialytic change ( $\Delta$ OER) is associated with an increased risk of intradialytic hypotension and mortality [10,11]. These pilot monocentric studies in small populations propose OER as a tool for monitoring the intradialytic stress and identifying an increased clinical risk in patients undergoing HD treatment via a central venous catheter (CVC). At present, large-population clinical studies able to confirm this hypothesis are lacking.

This study aimed to evaluate whether the intradialytic  $\Delta$ OER could identify patients with a higher mortality risk in a large population of HD patients with CVCs.

## 2. Methods

We conducted a prospective, multicentre, observational study involving patients receiving HD treatment thrice weekly by means of a CVC. The study protocol was approved by the local ethics committee (prot. N°850/18, Sapienza University ethics review board). Informed consent was obtained from all eligible patients. The inclusion criteria were an age  $\geq$  18 years, undergoing chronic HD treatment for at least 3 months via a permanent jugular CVC, and no evidence of an acute underlying illness nor of any active cancer. The exclusion criteria were less than 3 months of follow-up, presence of an arteriovenous fistula, evidence of a displaced or malfunctioning CVC (checked with chest radiography and CVC recirculation tests), chronic obstructive pulmonary disease, or a peripheral oxygen saturation (SpO<sub>2</sub>)  $<$ 90% in the resting condition. In addition, patients with severe refractory anaemia (haemoglobin [Hb]  $<$ 9 g/dl despite adequate erythropoietin administration and iron supplement therapy), congestive heart failure (New York Heart Association [NYHA] class  $\geq$  II), and severe peripheral vascular ischaemia were excluded. The planned recruitment time was 1 month, and the follow-up time was 2 years. We evaluated OER monthly in the first HD session of the week (after the long interdialytic interval) before and after HD during the 2 years of follow-up. During the follow-up, we recorded deaths and their causes in the study population. OER and  $\Delta$ OER, the difference between the OER after and before HD, were calculated using the following formulae:

$$OER = [(SpO_2 - ScvO_2) / SpO_2] \times 100$$

$$\Delta OER = [(OER_x - OER_0) / OER_0] \times 100,$$

where T<sub>0</sub> is the pre-HD OER and T<sub>x</sub> is the value obtained at the end of the HD session.

To evaluate the relationship between  $\Delta$ OER and the mortality risk, we divided the population according to the  $\Delta$ OER value calculated at the first measurement after inclusion in the study. The threshold  $\Delta$ OER was 40%, as previously identified [11]. SpO<sub>2</sub> levels were monitored using a peripheral pulse oximetry device. Patients wore a finger oximeter during the HD OER sessions, and SpO<sub>2</sub> values were recorded at established times. The blood sample to evaluate the pre-HD ScvO<sub>2</sub> was drawn from the arterial line of the CVC after discarding 20 mL of blood and before connecting to the extracorporeal circuit. The post-HD ScvO<sub>2</sub> was sampled from the arterial line of the dialysis circuit at the end of the dialysis session. Blood gas analysis was immediately performed using dedicated equipment. To

avoid pre-analytical artefacts, the handling of the blood for gas analysis was standardised according to the manufacturer's instructions. Blood for biochemical analysis was sampled at the beginning of the hemodialysis session when OER was measured for the first time. All patients received standard bicarbonate dialysis, according to their individual prescriptions of electrolyte concentrations, dialysate temperature (35.5–36.0 °C), and blood and dialysate flows. The HD OER sessions lasted 4 h, during which the patients fasted. The dialyser membrane was polyarylethersulfone, with a surface tailored to the patient's body surface. All patients were connected to the extracorporeal circuit without initial haemorrhage.

### 2.1. Ethical Standards

All procedures involving humans in this study were conducted in accordance with common and standard clinical practice, institutional and/or national research committees, and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

### 2.2. Statistical Analysis

Data are expressed as mean  $\pm$  standard deviation (SD) or median  $\pm$  inter quartile range (IQR). We evaluated the association of OER with time-to-event outcomes from the date of first HD treatment after the enrolment through stratified Kaplan–Meier curves and associated log-rank tests and/or univariate Cox regression models. Multivariate analyses used Cox regression models, where the final set of predictors was selected by means of forward selection based on the Akaike information criterion, subject to an upper bound of three predictors to be included. The upper bound was used to have at most fifteen events per predictor. All tests were two tailed, and (adjusted)  $p$ -values  $< 0.05$  were considered statistically significant. The final multivariate model actually included only two predictors. All analyses were performed using the open-source software package R version 4.2.2.

## 3. Results

Between 1 January 2019 and 31 January 2019, we evaluated 140 patients with CVCs from 4 Italian HD centres. A total of 101 patients (age,  $72.9 \pm 13.6$  years; HD vintage,  $9.6 \pm 16.6$  years; 61 males and 40 females) were included in the study. Thirty-nine patients were excluded for the presence of an arteriovenous fistula ( $n = 10$ ),  $\text{SpO}_2 < 90\%$  in the resting condition ( $n = 9$ ), and  $< 3$  months of follow-up ( $n = 20$ ).

The 101 patients, whose characteristics are shown in Table 1, were followed up for  $11.6 \pm 7.5$  months. Of these, 32% had diabetes, 70% had arterial hypertension, and 44% had previous vascular disease (defined as hypertension, ischaemic heart disease, and peripheral vasculopathy). In this population, at the first measurement after enrolment, the pre-HD OER was  $30.8 \pm 8.1$  (normal OER averages 20–30%) with a mean  $\Delta\text{OER}$  of  $42.3 \pm 34.8\%$  (Table 1). In the monthly assessment of OER during follow-up, the pre-HD OER and  $\Delta\text{OER}$  values were stable (Figure 1). As required by the protocol, to assess the role of the intradialytic increase in the OER ( $\Delta\text{OER}$ ) on mortality, we divided the population into two groups based on baseline measured  $\Delta\text{OER}$  values (threshold of 40%). The characteristics of the two groups are presented in Table 1. The two groups ( $\Delta\text{OER} \geq 40\%$ ,  $n = 45$ ;  $\Delta\text{OER} < 40\%$ ,  $n = 56$ ) did not differ in age, dialysis vintage, and prevalence of comorbidities. The evaluated haemodynamic, biochemical, and dialysis efficiency parameters were also not significantly different between the two groups (Table 1). The  $\Delta\text{OER} \geq 40\%$  group had a higher pre-HD  $\text{ScvO}_2$  ( $69.3 \pm 11.3$  vs.  $65.4 \pm 9.5$ ;  $p = 0.001$ ), lower post-HD  $\text{ScvO}_2$  ( $50.5 \pm 10.5$  vs.  $60.3 \pm 10.5$ ;  $p < 0.001$ ), lower pre-HD OER ( $27.1 \pm 5.6$  vs.  $33.8 \pm 8.6$ ;  $p < 0.001$ ), and higher post-HD OER ( $46.1 \pm 9.7$  vs.  $39.8 \pm 10.1$ ;  $p < 0.001$ ) (Table 1 and Figure 2). During the follow-up, 27 patients (60%) died in the  $\Delta\text{OER} \geq 40\%$  group, compared with 17 patients (30%) in the  $\Delta\text{OER} < 40\%$  group ( $p = 0.005$ , Table 1). The survival curve confirmed a lower survival in the  $\Delta\text{OER} \geq 40\%$  group (log-rank test:  $p < 0.001$ , Figure 3). The causes of death had different prevalence rates in the two groups (Figure 4), with a greater prevalence of cancer deaths in the  $\Delta\text{OER} \geq 40\%$  group ( $p = 0.04$ , Figure 4).

**Table 1.** Clinical and biochemical characteristics of the enrolled population and of the two sub-groups ( $\Delta\text{OER} \geq 40\%$  and  $\Delta\text{OER} < 40\%$ ).

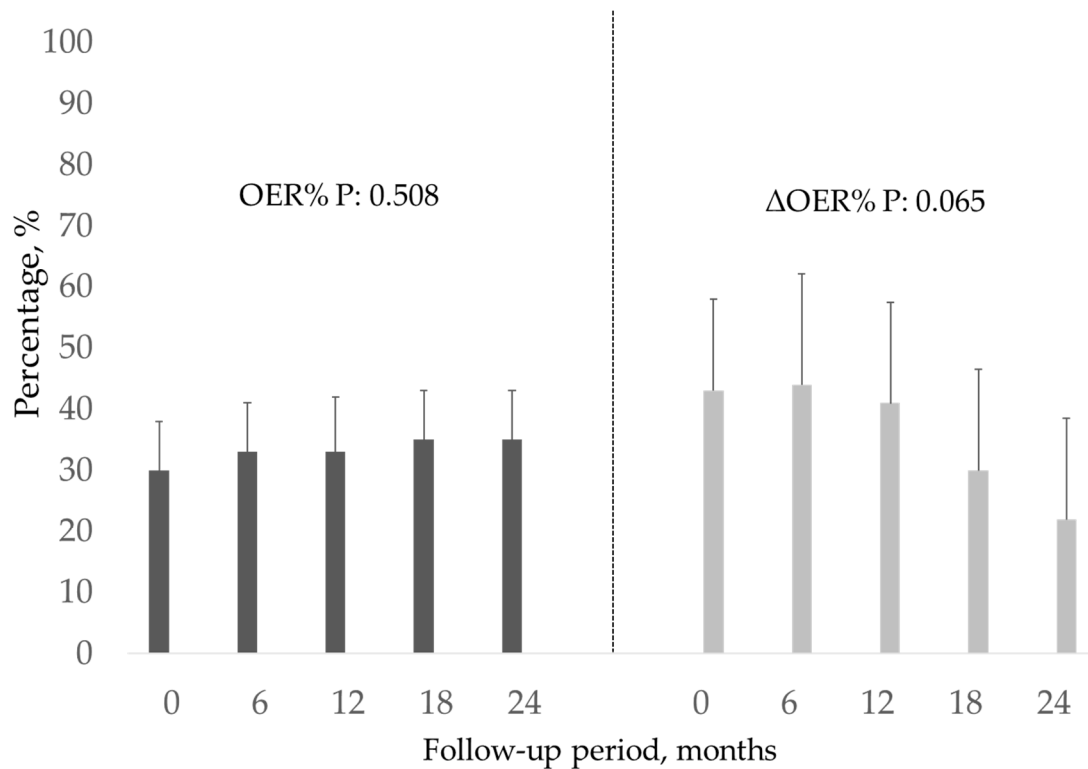
|                                  | Enrolled Population<br>(n = 101) | $\Delta\text{OER} \geq 40\%$<br>(n = 45) | $\Delta\text{OER} < 40\%$<br>(n = 56) | p Value |
|----------------------------------|----------------------------------|--|---------------------------------------|---------|
| Male/female, n (%)               | 61 (60%)/40 (40%)                | 28 (62)/17 (38)                          | 33 (58)/23 (42)                       | 0.535 * |
| Age, years                       | 72.9 ± 13.6                      | 70.6 ± 12.5                              | 74.7 ± 14.3                           | 0.240   |
| Vintage HD, years                | 9.6 ± 16.7                       | 8.2 ± 15.4                               | 10.7 ± 18.0                           | 0.490   |
| BMI (kg/m <sup>2</sup> )         | 23.1 ± 2.5                       | 24.9 ± 2.1                               | 25.6 ± 4.1                            | 0.630   |
| Diabetes mellitus, n (%)         | 32 (32)                          | 15 (33)                                  | 17 (30)                               | 0.525 * |
| HT, n (%)                        | 70 (70)                          | 33 (70)                                  | 37 (66)                               | 0.545 * |
| Vascular comorbidities °, n (%)  | 44 (44)                          | 20 (44)                                  | 24 (43)                               | 0.830 * |
| IV Erythropoietin therapy, n (%) | 94 (93)                          | 42 (92)                                  | 52 (93)                               | 0.935 * |
| IV iron therapy, n (%)           | 94 (93)                          | 42 (92)                                  | 52 (93)                               | 0.935 * |
| Pre-HD systolic BP, mmHg         | 131.4 ± 23.1                     | 131.7 ± 27.6                             | 131.1 ± 19.0                          | 0.930   |
| Pre-HD diastolic BP, mmHg        | 69.6 ± 11.8                      | 71.4 ± 12.2                              | 68.2 ± 11.5                           | 0.275   |
| Post-HD systolic BP, mmHg        | 133.2 ± 19.7                     | 131.9 ± 18.7                             | 134.3 ± 20.6                          | 0.645   |
| Post-HD diastolic BP, mmHg       | 71.1 ± 11.3                      | 72.6 ± 10.5                              | 69.9 ± 11.9                           | 0.230   |
| Pre-HD HR, bpm                   | 69.9 ± 10.8                      | 71.6 ± 11.1                              | 68.6 ± 10.5                           | 0.240   |
| Post-HD HR, bpm                  | 71.2 ± 10.4                      | 72.7 ± 10.1                              | 69.9 ± 10.7                           | 0.250   |
| Hb, g/dL                         | 10.6 ± 1.3                       | 10.6 ± 1.5                               | 10.5 ± 1.3                            | 0.730   |
| CRP, mg/dL                       | 1.5 ± 2.0                        | 1.4 ± 2.2                                | 1.8 ± 1.5                             | 0.240   |
| Ferritin, mcg/L                  | 316.9 ± 200.1                    | 320.3 ± 200.5                            | 300.2 ± 150.5                         | 0.155   |
| Albumin, g/dL                    | 3.4 ± 0.4                        | 3.3 ± 0.5                                | 3.4 ± 0.3                             | 0.340   |
| Ca, mg/dL                        | 8.7 ± 0.7                        | 8.7 ± 0.6                                | 8.7 ± 0.7                             | 0.985   |
| P, mg/dL                         | 5.1 ± 1.4                        | 5.3 ± 1.4                                | 5.1 ± 1.4                             | 0.530   |
| PTH, pg/mL                       | 347.9 ± 247.8                    | 360.4 ± 287.6                            | 337.6 ± 212.4                         | 0.740   |
| KT/V                             | 1.3 ± 0.2                        | 1.3 ± 0.2                                | 1.3 ± 0.2                             | 1.000   |
| Total UF, mL                     | 607.1 ± 193.2                    | 632.5 ± 197.4                            | 586.3 ± 188.5                         | 0.435   |
| UF, mL/h/kg                      | 8.3 ± 3.3                        | 8.1 ± 3.2                                | 8.4 ± 3.4                             | 0.650   |
| ScvO <sub>2</sub> pre-HD, %      | 67.1 ± 9.5                       | 69.3 ± 11.3                              | 65.4 ± 9.5                            | 0.001   |
| ScvO <sub>2</sub> post-HD, %     | 55.2 ± 11.3                      | 50.5 ± 10.5                              | 60.3 ± 10.5                           | <0.001  |
| SaO <sub>2</sub> pre-HD, %       | 98.1 ± 3.5                       | 98.5 ± 3.1                               | 98.2 ± 2.1                            | 0.930   |
| SaO <sub>2</sub> post HD, %      | 97.2 ± 3.1                       | 97.0 ± 3.0                               | 97.0 ± 2.0                            | 0.945   |
| OER pre-HD                       | 30.8 ± 8.1                       | 27.1 ± 5.6                               | 33.8 ± 8.6                            | <0.001  |
| OER post-HD                      | 42.3 ± 13.8                      | 46.1 ± 9.7                               | 39.8 ± 10.1                           | <0.001  |
| $\Delta\text{OER}$ , %           | 42.3 ± 34.8                      | 70.4 ± 25.3                              | 19.7 ± 11.6                           | <0.001  |
| Follow-up, months                | 11.6 ± 7.5                       | 11.1 ± 6.6                               | 12.1 ± 8.1                            | 0.505   |
| Death, n (%)                     | 44 (44)                          | 27 (60)                                  | 17 (30)                               | 0.005 * |
| Annual mortality rate, %         | 20                               | 30                                       | 15                                    | 0.005 * |
| Causes of death                  |                                  |  |                                       |         |
| Cardiovascular, n (%)            | 20 (45)                          | 10 (37)                                  | 10 (59)                               | 0.135   |
| Cancer, n (%)                    | 12 (27)                          | 11 (41)                                  | 1 (5)                                 | 0.040   |
| Infection, n (%)                 | 12 (27)                          | 6 (22)                                   | 6 (35)                                | 0.430   |

Data are expressed as mean ± SD. HD, haemodialysis; BMI, body mass index; HT, hypertension; BP, blood pressure; MAP, mean arterial pressure; HR, heart rate; Hb, Haemoglobin; CRP, C-reactive protein; Ca, calcium; P, phosphate; PTH, serum parathormone; UF, ultrafiltration rate; ScvO<sub>2</sub>, central venous SO<sub>2</sub>; SaO<sub>2</sub>, arterial SO<sub>2</sub>; OER, oxygen extraction ratio;  $\Delta\text{OER}$ , variation in OER; IV: intravenous; ° Vascular comorbidities: hypertension, ischaemic heart disease, and peripheral vasculopathy.  $\Delta\text{OER} < 40\%$  vs.  $\Delta\text{OER} \geq 40\%$ ; \* Chi-squared test for qualitative variables. T-test for quantitative variables were used to compare measurements between groups.

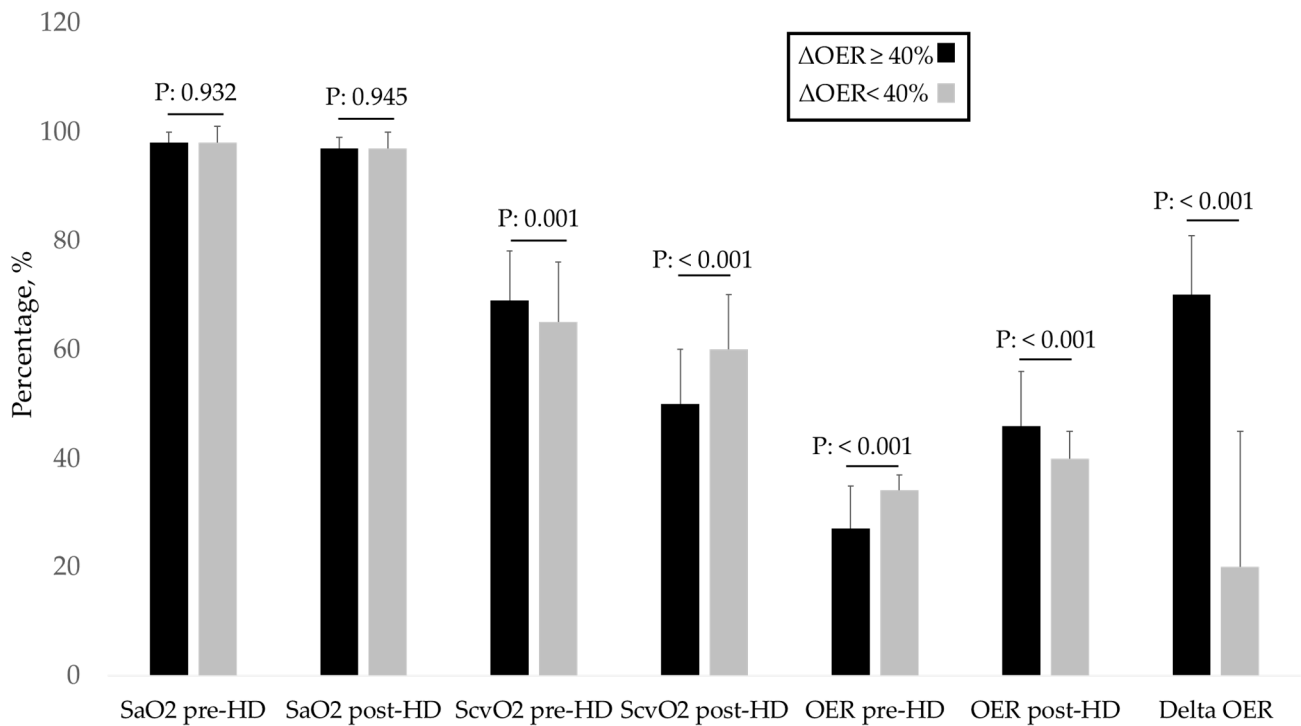
The multivariate analysis showed that a  $\Delta\text{OER}$  of  $\geq 40\%$  ( $p = 0.0002$ ) and heart rate ( $p = 0.001$ ; Table 2) were the best independent predictors of mortality risk in the study population.

The characteristics of the 44 patients who died are shown in Table 3. The 44 non-survivors were compared with survivors and showed lower dialysis vintage ( $4.5 \pm 8.1$  vs.  $14.7 \pm 21.1$ ,  $p = 0.01$ ), higher heart rates before ( $72.7 \pm 9.8$  vs.  $67.9 \pm 11.1$ ,  $p = 0.03$ ) and after HD ( $75.4 \pm 9.2$  vs.  $68.9 \pm 10.2$ ,  $p = 0.003$ ), and lower albuminemia levels ( $3.2 \pm 0.4$  vs.  $3.5 \pm 0.3$ ,  $p = 0.001$ ). Regarding the oxygen parameters evaluated, the non-survival group had a lower post-HD ScvO<sub>2</sub> ( $52.3 \pm 11.2$  vs.  $58.4 \pm 10.2$ ,  $p = 0.01$ ) and post-HD OER

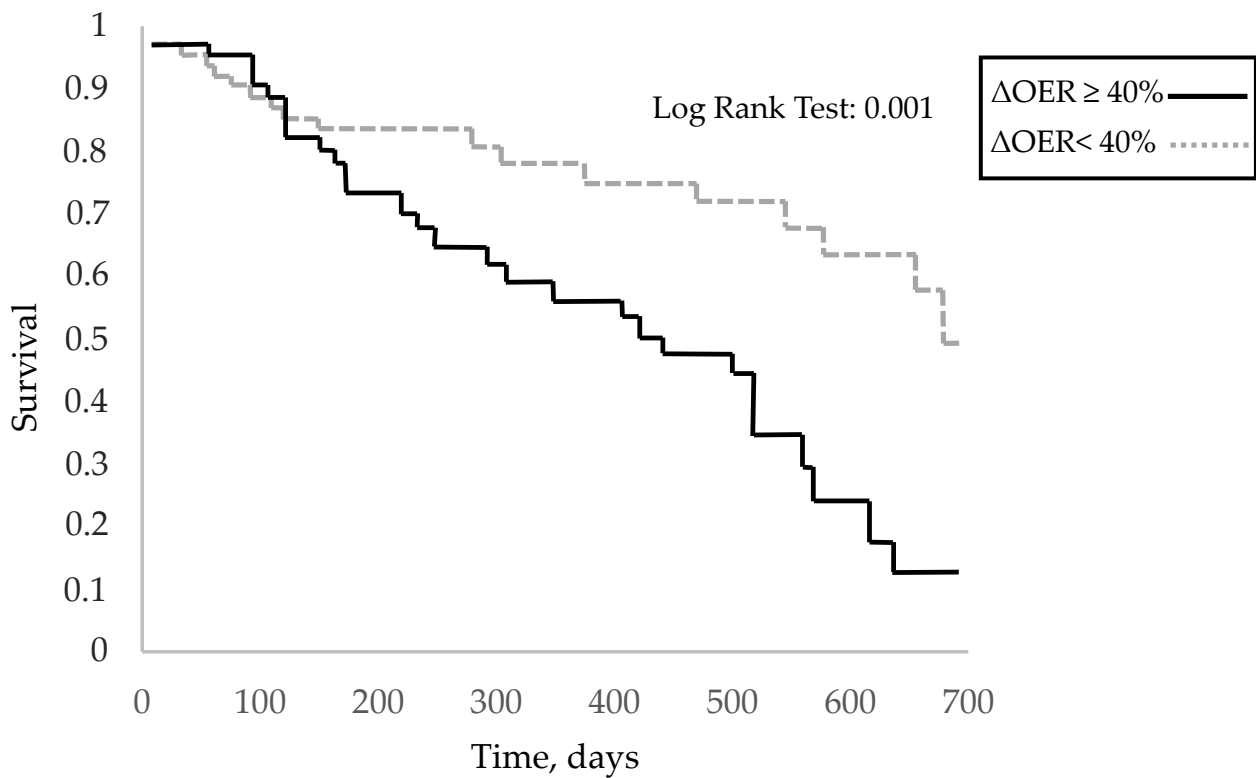
( $45.5 \pm 9.8$  vs.  $39.9 \pm 10.4$ ,  $p = 0.01$ ) and a greater dialytic  $\Delta$ OER ( $45.3 \pm 25.7$  vs.  $40.0 \pm 36.0$ ,  $p = 0.02$ ) than those in the survival group (Table 3).



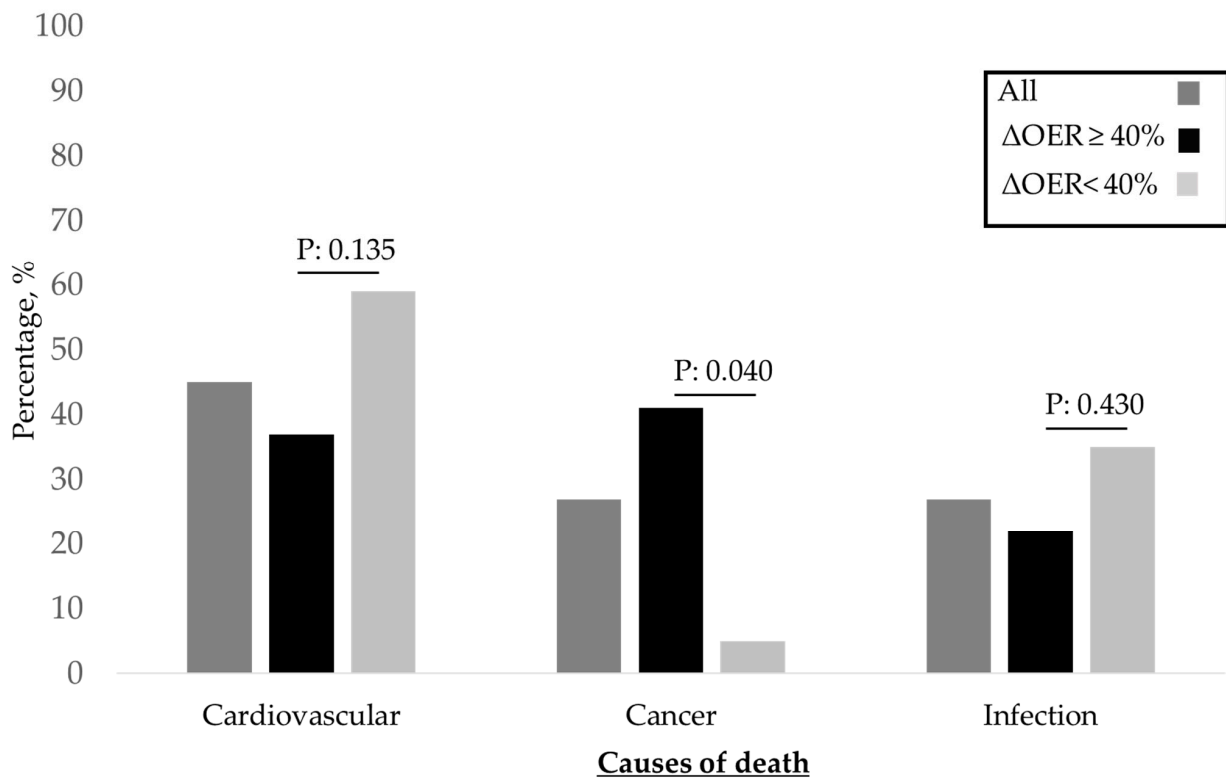
**Figure 1.** OER pre-HD and  $\Delta$ OER during the follow-up. OER, oxygen extraction ratio;  $\Delta$ OER, variation in OER.



**Figure 2.** Oxygen parameter in the two groups  $\Delta$ OER  $\geq$  40% and  $\Delta$ OER < 40%. ScvO2, central venous SO2; SaO2, arterial SO2; OER, oxygen extraction ratio;  $\Delta$ OER, variation in OER.



**Figure 3.** Overall survival,  $\Delta\text{OER} \geq 40\%$  vs.  $\Delta\text{OER} < 40\%$ . Time 0 was the date of the first haemodialysis session after enrolment. Kaplan–Meier log rank test,  $p = 0.001$ . OER, oxygen extraction ratio;  $\Delta\text{OER}$ , variation in OER.



**Figure 4.** Incidence of causes of death in the entire population and in the  $\Delta\text{OER} \geq 40\%$  and  $\Delta\text{OER} < 40\%$  groups. OER, oxygen extraction ratio;  $\Delta\text{OER}$ , variation in OER.

**Table 2.** Univariate and multivariate survival analysis of the enrolled population (N = 101).

| Univariate Survival Analyses   |      |         |        |        |
|--------------------------------|------|---------|--------|--------|
| Variable                       | HR   | C.I.low | C.I.up | p      |
| Age, years                     | 1.01 | 0.99    | 1.04   | 0.360  |
| Vintage HD, years              | 0.97 | 0.92    | 1.02   | 0.255  |
| OER pre-HD                     | 0.97 | 0.93    | 1.01   | 0.165  |
| OER post-HD                    | 1.02 | 0.98    | 1.05   | 0.295  |
| Delta OER %                    | 1.01 | 1.00    | 1.02   | 0.100  |
| Delta OER % ≥40%               | 2.76 | 1.46    | 5.22   | <0.001 |
| Pre-HD systolic BP, mmHg       | 1.00 | 0.99    | 1.01   | 0.745  |
| Pre-HD diastolic BP, mmHg      | 1.00 | 0.97    | 1.02   | 0.940  |
| Pre-HD HR, bpm                 | 1.03 | 1.00    | 1.06   | 0.030  |
| Post-HD systolic BP, mmHg      | 0.99 | 0.98    | 1.01   | 0.475  |
| Post-HD diastolic BP, mmHg     | 1.00 | 0.97    | 1.03   | 0.930  |
| Post-HD HR, bpm                | 1.05 | 1.01    | 1.08   | 0.001  |
| Uf h, mL                       | 0.99 | 0.99    | 0.99   | 0.010  |
| Uf mL/min/Kg                   | 0.88 | 0.80    | 0.98   | 0.020  |
| Hb g/dL                        | 0.90 | 0.71    | 1.15   | 0.410  |
| Ca mg/dL                       | 0.86 | 0.52    | 1.40   | 0.540  |
| P mg/dL                        | 0.94 | 0.74    | 1.20   | 0.635  |
| PTH ng/mL                      | 1.00 | 1.00    | 1.00   | 0.490  |
| Diabetes (no-yes)              | 1.23 | 0.66    | 2.31   | 0.510  |
| CVC (no-Yes)                   | 1.00 | 0.53    | 1.89   | 0.990  |
| CRP                            | 1.00 | 0.98    | 1.01   | 0.990  |
| Albuminemia                    | 1.03 | 0.99    | 1.08   | 0.155  |
| KT/V                           | 0.21 | 0.04    | 1.03   | 0.060  |
| Multivariate Survival Analyses |      |         |        |        |
| Variable                       | HR   | C.I.low | C.I.up | p      |
| Delta OER % ≥40%               | 2.76 | 1.46    | 5.22   | <0.001 |
| Post-HD HR, bpm                | 1.05 | 1.01    | 1.08   | 0.001  |

ΔOER, variation in OER; HD, haemodialysis; BP, blood pressure; HR, heart rate, UF, ultrafiltration rate; Hb, Haemoglobin; CRP, C-reactive protein; ScvO<sub>2</sub>, central venous, SO<sub>2</sub>; SaO<sub>2</sub>, arterial SO<sub>2</sub>; OER, oxygen extraction ratio; CVC, central venous catheter; UF, ultrafiltration; C.I., confidence interval.

**Table 3.** Characteristics of survivors and non-survivors.

|                                 | Survivors (n = 57) | Non-Survivors (n = 44) | p-Value |
|---------------------------------|--------------------|------------------------|---------|
| Male/female, n (%)              | 33 (57)/24 (43)    | 28 (63)/16 (37)        | 0.535 * |
| Age, years                      | 70.4 ± 14.9        | 75.5 ± 11.8            | 0.110   |
| Vintage HD, years               | 14.7 ± 21.1        | 4.5 ± 8.1              | 0.010   |
| BMI (kg/m <sup>2</sup> )        | 25.2 ± 3.1         | 24.2 ± 2.1             | 0.835   |
| Diabetes mellitus, n (%)        | 15 (26)            | 17 (38)                | 0.535 * |
| HT, n (%)                       | 40 (70)            | 30 (68)                | 0.520 * |
| Vascular comorbidities °, n (%) | 29 (51)            | 15 (34)                | 0.545 * |
| Pre-HD systolic BP, mmHg        | 132.3 ± 26.4       | 130.1 ± 18.1           | 0.640   |
| Pre-HD diastolic BP, mmHg       | 70.1 ± 11.6        | 69.0 ± 12.4            | 0.661   |
| Post-HD systolic BP, mmHg       | 135.4 ± 21.4       | 130.4 ± 17.2           | 0.210   |
| Post-HD diastolic BP, mmHg      | 71.0 ± 11.8        | 71.2 ± 10.7            | 0.985   |
| Pre-HD HR, bpm                  | 67.9 ± 11.1        | 72.7 ± 9.8             | 0.030   |
| Post-HD HR, bpm                 | 68.9 ± 10.2        | 75.4 ± 9.2             | 0.003   |
| Hb, g/dL                        | 10.8 ± 1.4         | 10.2 ± 14.4            | 0.061   |
| CRP, mg/dL                      | 1.6 ± 1.5          | 1.6 ± 2.2              | 0.991   |
| Ferritin, mcg/L                 | 310.2 ± 150.5      | 310.3 ± 200.5          | 0.990   |
| Albumin, g/dL                   | 3.5 ± 0.3          | 3.2 ± 0.4              | 0.001   |
| Ca, mg/dL                       | 8.8 ± 0.7          | 8.5 ± 0.6              | 0.060   |
| P, mg/dL                        | 5.2 ± 1.4          | 5.1 ± 1.3              | 0.630   |
| PTH, pg/mL                      | 363.1 ± 294.3      | 330.5 ± 187.4          | 0.575   |



Table 3. Cont.

|                              | Survivors (n = 57) | Non-Survivors (n = 44) | p-Value |
|------------------------------|--------------------|------------------------|---------|
| KT/V                         | 1.35 ± 0.2         | 1.32 ± 0.2             | 0.230   |
| UF, mL/h                     | 650.1 ± 189.1      | 551.3 ± 202.0          | 0.080   |
| UF, mL/h/kg                  | 9.4 ± 2.9          | 7.2 ± 3.4              | 0.095   |
| ScvO <sub>2</sub> pre-HD, %  | 68.3 ± 8.5         | 67.3 ± 10.3            | 0.835   |
| ScvO <sub>2</sub> post-HD, % | 58.4 ± 10.2        | 52.3 ± 11.2            | 0.010   |
| SaO <sub>2</sub> pre-HD, %   | 98.4 ± 1.8         | 98.2 ± 2.2             | 0.990   |
| SaO <sub>2</sub> post HD, %  | 97.5 ± 2.0         | 97.3 ± 1.8             | 0.995   |
| OER pre-HD                   | 30.2 ± 8.4         | 31.6 ± 7.7             | 0.370   |
| OER post-HD                  | 39.9 ± 10.4        | 45.5 ± 9.8             | 0.015   |
| ΔOER, %                      | 40.0 ± 36.0        | 45.3 ± 25.7            | 0.040   |
| Follow-up, months            | 12.3 ± 7.5         | 10.7 ± 7.4             | 0.275   |
| Causes of death              |                    |                        |         |
| Cardiovascular, n (%)        |                    | 20 (45)                |         |
| Cancer, n (%)                |                    | 12 (27)                |         |
| Infection, n (%)             |                    | 12 (27)                |         |

Data are expressed as mean ± SD. HD, haemodialysis; BMI, body mass index; HT, hypertension; BP, blood pressure; MAP, mean arterial pressure; HR, heart rate; Hb, Haemoglobin; CRP, C-reactive protein; Ca, calcium; P, phosphate; PTH, serum parathormone; UF, ultrafiltration rate; ScvO<sub>2</sub>, central venous SO<sub>2</sub>; SaO<sub>2</sub>, arterial SO<sub>2</sub>; OER, oxygen extraction ratio; ΔOER, variation in OER; ° Vascular comorbidities: hypertension, ischaemic heart disease, and peripheral vasculopathy; \* Chi-squared test for qualitative variables. T-test for quantitative variables were used to compare measurements between groups.

#### 4. Discussion

This prospective multicentre study showed that a ≥40% increase in oxygen extraction during HD, measured using ΔOER%, identified patients with an increased risk of mortality during an average follow-up of 11.6 months.

This study enrolled 101 patients (average age, 72.9 years) with CVCs undergoing chronic HD treatment for 9.6 ± 16.6 years (Table 1) and evaluated the pre- and post-HD OER to obtain the intradialytic ΔOER. OER is obtained from the ratio of the central venous saturation to the arterial oxygen saturation, which measures the O<sub>2</sub> parenchymal extraction better than the ScvO<sub>2</sub> alone. In fact, the ScvO<sub>2</sub> might change even in the case of arterial hypoxia, and in this case, its change does not represent a measure of parenchymal O<sub>2</sub> extraction, especially in clinical conditions where SaO<sub>2</sub> might change, as occurs during HD sessions [12]. For these reasons, OER is a more reliable parameter for monitoring parenchymal oxygen needs and use in HD patients [10]. In our population, the pre-HD OER was 30.8 ± 8.1%, which was within the normal range (20–30%). However, the OER increased during HD sessions, with a post-HD OER of 42.3 ± 13.8% and a ΔOER of 42.3 ± 34.8% (Table 1). This result confirms that during HD sessions, there is an increase in the extraction of parenchymal O<sub>2</sub>, characterised by a stability of the arterial oxygen saturation and a reduction of the ScvO<sub>2</sub> (Table 1). This result is consistent with the evidence in the literature showing that hypoxic parenchymal stress develops during HD sessions [13,14]. This hypoxic parenchymal stress requires an increased oxygen extraction, which can be monitored using the OER [8]. Importantly, all OER sessions in the patients were in the absence of symptoms and evident changes in the blood pressure and heart rate (Table 1). It is important to note that OER and ΔOER values were stable over time (Figure 1) in our population, as already evidenced in previous studies [11]. This stability is crucial for rendering OER a clinically useful monitoring parameter. During the follow-up of 11.6 months, we recorded 44 deaths in the population, with an annual mortality of 20%. Of the deaths, 45%, 27%, and 27% were from cardiovascular, infectious, and neoplastic causes, respectively (Figure 4). This result is consistent with what is known in the literature on CVC HD patients, both in terms of the absolute mortality and the incidence of different causes of death [15]. Thus, our study population is representative of the general CVC HD patients in terms of mortality and causes of death. The main purpose of our study was to assess whether a high intradialytic ΔOER (40% threshold) is a risk factor for mortality in



HD patients. This hypothesis is derived from the evidence that the hypoxic tissue stress that develops during an HD session causes alterations of organ functions, resulting in chronic organ damage and increased mortality [8]. In agreement with Chan et al., patients at greater clinical risk were identified as those with a greater ScvO<sub>2</sub> reduction [16]. Furthermore, a pilot study of 20 patients identified the intradialytic  $\Delta$ OER as a possible risk factor for mortality [11]. To verify the above hypothesis, we divided our population of 101 patients into two groups based on the first  $\Delta$ OER value measured after enrolment in the study. The limit of the  $\Delta$ OER used to identify the two groups was decided by the protocol to be 40% based on the data in the literature [11]. We dichotomised our population into two groups:  $\Delta$ OER  $\geq$  40 and  $\Delta$ OER < 40%. As shown in Table 1, the two groups were clinically similar (same age, dialytic history, comorbidity, and dialytic efficiency), but the group with a  $\Delta$ OER of  $\geq$ 40% had a mortality of 60%, compared with 30% in the group with a  $\Delta$ OER of <40% ( $p = 0.005$ , Table 1). This was confirmed by the survival curve (Figure 3), which showed that patients with a  $\Delta$ OER of  $\geq$ 40% had increased mortality (log-rank test:  $p = 0.001$ ), and multivariate analysis, which highlighted a  $\Delta$ OER of  $\geq$ 40% as an independent risk factor in the studied population (Table 2). These results agree with other evidence confirming that patients who need to significantly increase oxygen extraction by the parenchyma during HD have a higher mortality risk, probably secondary to the increased chronic hypoxic parenchymal damage linked to the haemodialytic stress [17]. The change in oxygen extraction in our patients was not caused by a change in SaO<sub>2</sub>, which remained unchanged (Table 1), but by an increase in the parenchymal extraction, which resulted in a reduction of the ScvO<sub>2</sub> and therefore an increase in the OER (Figure 2). An interesting fact that confirms what has already been highlighted in the literature [11] is that the  $\Delta$ OER  $\geq$  40% group had a lower pre-HD OER (Table 1, Figure 2). These data may suggest that these patients have a lower adaptation to the uraemic condition. In fact, patients with ESRD have a chronic impairment of the ability to use and distribute O<sub>2</sub> secondary to a reduction of the capillary bed and mitochondrial dysfunction [8,18,19]. According to various studies, the basal ScvO<sub>2</sub> of patients undergoing HD is lower than expected because of the increased need for basal oxygen extraction in this population [17]. The presence of normal O<sub>2</sub> extraction in a uraemic population can indicate a maladjustment to the condition, resulting in a large increase in the O<sub>2</sub> extraction during the HD session. Patients who developed lower hypoxic stress ( $\Delta$ OER < 40% group) during the haemodialytic session had a basally increased OER, a sign of a better adaptation to the uraemic state (Figure 2). Interestingly, the causes of death in the two groups studied ( $\Delta$ OER  $\geq$  40% and <40%) had different incidences (Figure 4). In particular, the group with a  $\Delta$ OER of  $\geq$ 40% had an increased risk of mortality due to neoplastic causes (Figure 4,  $p = 0.04$ ). These data are in agreement with the experimental evidence showing that intermittent hypoxia, such as that present in our patients, increases the risk of cancer [20,21]. This explains, at least in part, the increased presence of cancer in the group with increased intradialytic parenchymal hypoxia (Figure 4).

Retrospectively assessing the differences between the non-survival ( $n = 44$ ) and survival ( $n = 57$ ) populations showed that non-survivors had a shorter dialysis history, lower albuminemia, and a higher average  $\Delta$ OER and heart rate (Table 3). These data confirm some well-known risk factors in HD patients, such as low albuminemia and a high heart rate [22,23]. In particular, one of the parameters that changes in the case of tissue hypoxaemia is the heart rate, and our data showed that patients at greater risk of mortality had a higher heart rate and higher oxygen extraction during the HD treatment. According to our data, we identified two types of patients: those adapted to the uraemic state and those that were not adapted or maladjusted. The characteristics of this last typology of patients, with an increased risk of mortality, are an intradialytic  $\Delta$ OER  $\geq$  40%, a lower pre-HD OER, a higher basal heart rate, and a shorter HD history. A major limitation of the OER measurement technique is that it can be exclusively applied to patients with CVC and without a fistula. However, recent evidence showed that CVC use in HD is nonetheless necessary in 50–60% of patients with poor vascular systems who are also fragile and have higher mortality rates (9). In these patients, the  $\Delta$ OER could be an easily measurable parameter

applicable in clinical practice to highlight the most fragile patients. This would allow us to act on these patients with targeted therapies. Another limitation of the study was that, due to the observational nature of the protocol, it was not possible to verify if the intradialytic  $\Delta$ OER could be reduced by therapeutic interventions (e.g., modulation of intradialytic ultrafiltration, pre-HD physical activity, pharmacological heart rate modulation). This is a very interesting and important point and future interventional studies are needed to assess whether the  $\Delta$ OER can be reduced with therapeutic actions.

In conclusion, our data showed that patients who develop greater parenchymal hypoxic damage during HD treatment have an increased mortality risk and that the measurement of the OER and intradialytic  $\Delta$ OER can highlight the development of this critical hypoxic damage.

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