Interaction between parathyroid hormone and the Charlson comorbidity index on survival of incident haemodialysis patients

Luigi Francesco Morrone1, Sandro Mazzaferrro2, Domenico Russo3, Filippo AuCella4, Mario Cozzolino5, Maria Grazia Facchini6, Andrea Galfre7, Fabio Malberti8, Maria Cristina Mereu9, Maurizio Nordio10, Giovanni Pertosa11, Domenico Santoro12 and CPCP Study Investigators*

1 Renal Division, A.O. Rummo, 82100 Benevento, 2 Renal Division, Università ‘Sapienza’, 00161 Roma, 3 Renal Division, University Federico II, 80131 Napoli, 4 Renal Division, PO Lastarla, 71036 Lucera, 5 Renal Division, A.O. San Paolo Polo Universitario, Milano, 6 Renal Division, A.O. Sant’Orsola Malpighi, 40138 Bologna, 7 Renal Division, Dialisi Territoriale, 09100 Cagliari, 8 Renal Division, A.O. Istituti Ospitalieri, 26100 Cremona, 9 Renal Division, PO Nostra Signora di Bonaria, 09025 S. Gavino Monreale, 10 Renal Division, PO Campo San Piero, 35100 Padova, 11 Renal Division, Azienda Universitaria Ospedaliera Policlinico, 70124 Bari and 12 Renal Division, Università degli Studi di Messina, 98128 Messina, Italy

Correspondence and offprint requests to: Luigi Francesco Morrone; E-mail: l.morrone@fastwebnet.it

*Investigators of the CPCP (‘Comorbidity–Parathormone–Calcium–Phosphate’) study, belonging to the ‘Mineral Metabolism and Trace Elements’ study group of the Italian Society of Nephrology, are listed in the Appendix.

Abstract

Background. Haemodialysis patients are ageing and have with a high rate of comorbidities. The impact of this novel clinical setting on intact parathyroid hormone (iPTH) is not well established.

Methods. For this observational, prospective multicentre cohort study, incident haemodialysis patients were recruited in 40 Italian centres and followed up for a mean period of 18 ± 6.7 months. Clinical characteristics and biochemistry were recorded at baseline. Comorbid conditions were scored by the Charlson comorbidity index (CCI).

Results. Data of 411 patients (mean age: 66.5 ± 14.8 years; 17.3% > 80 years old) were recorded. The mean CCI was 4.17 ± 2.8. In patients with CCI > 0, an inverse correlation was observed between CCI (excluding age) and iPTH (P = 0.00002). Independently of CCI, patients with iPTH < 150 pg/ml had 76% as high as the risk
of all-cause mortality. After multivariable adjustment, the combination of the first tertile of iPTH with second and third tertiles of CCI was significantly associated with all-cause mortality (RR = 3.83, P = 0.02; RR = 3.79, P = 0.01, respectively).

Conclusions. Incident haemodialysis patients suffer from a high rate of clinical complications. In these patients, low iPTH and high CCI are often associated and very likely responsible for an adverse outcome.

Keywords: Charlson index; elderly; incident ESRD patients; intact parathyroid hormone; survival

Introduction

In most western countries, the median age of patients starting renal replacement therapy (RRT) has increased over the last decade with a concomitant rise in comorbidities and with diabetes as the leading cause of renal failure [1–5]. Other frequent comorbidities are cancer (11%), coronary, cerebral and/or peripheral vascular disease (61%) [6].

Comorbidities in ageing patients represent an emerging problem for nephrologists, and these make the management of patients in RRT even more difficult despite the progress in dialysis techniques [6,7]. Therefore, greater attention and specific research probably should be devoted to the above-mentioned comorbidities, going beyond the traditional role as a statistical adjustment tool in survival studies on patients with chronic kidney disease (CKD). For instance, the impact of comorbidities on some CKD complications such as the CKD-mineral bone disorder is unknown.

Comorbidities can be assessed in several ways. In the general population, the Charlson comorbidity index (CCI) is commonly used. In its original structure as well as in ensuing adaptations, the CCI is considered as a valid and easy to use method for assessing comorbidities and predicting survival also in incident patients with end-stage renal disease (ESRD) [8–12].

The present study aimed at investigating the relationship between comorbidities and intact parathyroid hormone as well as the impact of their interaction on survival in a cohort of incident haemodialysis patients.

Subjects and methods

The present observational cohort study was performed in 411 incident haemodialysis patients who started treatment between 13 January 2005 and 4 September 2007. Data were collected from 40 Italian renal units. The study has been exclusively managed by nephrologists belonging to the ‘Mineral Metabolism and Trace Elements study group’ of the Italian Society of Nephrology. The study was completely independent and did not receive support from any pharmaceutical or medical company. The STROBE recommendations for observational studies (http://www.strobe-statement.org) were taken into account.

Inclusion criteria

Consecutive patients (age ≥21 years) who started RRT in each participating centre during the 1-year enrolment period were allowed to enter the study. A further inclusion criterion was adequacy of dialysis dose according to K/DOQI guidelines (spKt/V >1.2, assessed using pre-dialysis and post-dialysis blood urea nitrogen sampling). Exclusion criteria were as follows: previous kidney transplant, switch from peritoneal dialysis and spKt/V ≤1.2 in two consecutive monthly measurements. During the 1-year enrolment period, 500 patients started RRT. The median number of patients for each centre was 9 (range 2–59). From the initial cohort, 15 patients did not fit inclusion criteria and 24 did not have complete data. Patients on peritoneal dialysis (n = 38) and those on haemodialysis on calcium in dialysate different from 1.50 mmol/l (n = 12) were excluded. Thus, 411 patients were recruited.

Data collection

Baseline data were as follows: patient identifying code, birth date, gender, underlying kidney disease, dialysis start date, duration of pre-dialysis follow-up, smoking habit, co-morbid conditions, ability to walk without assistance, systolic and diastolic blood pressure, anti-hypertensive drugs, treatment and dosages of vitamin D receptor activators (VDRA), calcimimetic and phosphate-binding drugs. In addition, the following laboratory data were recorded: serum calcium, phosphate, albumin and haemoglobin (determined within 1 month from the beginning of dialysis), concentration of serum intact parathyroid hormone (iPTH) (assayed within the first 2 months of dialysis using second generation methods) and C-reactive protein (C-rp) (assayed within the first 3 months of dialysis). The blood samples were collected using uniform techniques before the start of the first dialysis session of the week and were sent to the laboratory within 2 h, with the iPTH sample on ice. Serum total calcium was corrected for albuminaemia according to the formula: albumin – corrected calcium = measured calcium + (4.0 – serum albumin in g/dl) × 0.13 [13].

Patients with a positive history of hyperglycaemia and/or on chronic treatment with insulin or anti-diabetic drugs were regarded as diabetic. In accordance with the NJC-7 guidelines, hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg [14]. Patients with systolic pressure <90 mmHg were arbitrarily recorded as hypotensive. Patients with a pre-dialysis follow-up <4 months were labelled as ‘late referrals’ to the nephrology service [15].

The presence and degree of comorbid conditions were assessed using the CCI at the beginning of dialysis [8]. The CCI includes age (weight 1 for every 10 years starting from 40 years of age) and contains 17 categories of comorbidities including congestive heart failure (weight 1), myocardial infarction (weight 1), chronic pulmonary disease (weight 1), cerebrovascular disease (weight 1), haemiplegia or paraplegia (weight 2), dementia (weight 1), diabetes with complication (weight 2), malignancy (weight 2), metastatic solid tumour (weight 6), mild liver disease (weight 1), moderate or severe liver disease (weight 3), peptic ulcer disease (weight 1), peripheral vascular disease (weight 1), rheumatologic disease (weight 1), renal disease (weight 2) and AIDS (weight 6). In this study, the CCI score for the presence of kidney disease was not taken into account being all patients were on RRT.

The following cardiovascular events were recorded: stroke or transient ischaemic attack, angina pectoris or acute myocardial infarction, congestive heart failure, haemodynamically significant tachyarrhythmias or bradyarrhythmias, and dissecting aneurysms of the aorta.

Death due to one of the above events was recorded as death from cardiovascular causes. Other deaths were considered not due to cardiovascular causes.

The diagnosis of cardiovascular events was based on medical records obtained from participating centres and reviewed by the principal investigator of the study (L.F.M.).

Statistics

All data are presented as proportions of the patient population, mean ± standard deviation or median and range, as appropriate. Differences between groups were evaluated using the Kruskal–Wallis test, one-way ANOVA or χ² analysis, where necessary.

Due to the multicentre nature of the study, iPTH levels were assayed in different laboratories and with different commercial kits. Accordingly, we have applied a hierarchical multilevel regression approach that enabled us to take into account the centre and method effects. The multilevel model used included random intercepts and fixed slopes. The assumption is that the effects are fixed for centres and methods, whereas the mean effect of each hospital is allowed to vary [16]. A likelihood ratio (LR) test was used to evaluate the suitability of the single level versus multilevel regression approach. When the LR test was not applicable, the Wald test was used.
Comorbidities, n

Diabetes, n

Aetiology of ESRD, n

Autonomous walking impairment, n

Arterial hypertension, n

Age over 80 years, n

lying kidney diseases and most frequent comorbidities are

biopsy was performed only in 12% of all patients. Under-

tients did not have diabetic nephropathy (2%), but a renal

eraldy and had multiple co-morbidities. A few diabetic pa-

14.8 years) were enrolled. The patient characteristics at the

Study population

A total of 260 males and 151 females (mean age: 66.5 ±
14.8 years) were enrolled. The patient characteristics at the

start of RRT are presented in Table 1. Most patients were
erly and had multiple co-morbidities. A few diabetic pa-
dients did not have diabetic nephropathy (2%), but a renal

biopsy was performed only in 12% of all patients. Under-
lying kidney diseases and most frequent comorbidities are

also reported in Table 1. Figure 1 shows the distribution of

the CCI score in the whole cohort.

Baseline clinico-laboratory characteristics according to

iPTH levels

Tables 2 and 3 show the clinico-laboratory characteristics of

patients at the dialysis initiation according to iPTH. Patients

with low-to-normal iPTH levels had a significantly higher

rate of the CCI (excluding age) (P = 0.01) and diabetes

(P = 0.03). Patients with low iPTH displayed the highest

frequency of late referral (P = 0.005), high serum calcium

(P = 0.01) and low serum phosphate (P = 0.02). Patients

with iPTH >300 pg/ml had more frequently low serum
calcium levels (P = 0.001), and they were more frequently

treated with active forms of vitamin D (P = 0.0003). Among

patients with iPTH > 300 pg/ml, 25% (9% of the entire

cohort) had iPTH > 600 pg/ml.

Correlation between iPTH levels and CCI

Non-significant correlation between iPTH and CCI was

observed in the entire cohort. In contrast, the correla-
tion became significant when data of patients without com-

morbidities were not taken into account (rho = −0.12, P =

0.02). Of note, the statistical significance increased (rho =

−0.25, P = 0.00001) when age was excluded from the

CCI. The inverse correlation persisted (rho = −0.31, P =

0.001) when analysis was repeated in the subgroup of pa-
nents with comorbidities but younger than 65 years old.

Finally, the inverse correlation was confirmed in a multiple

regression model adjusted for serum calcium and phosphate

and active vitamin D administration; the highest correla-
tion (beta = −0.20, P = 0.0004) was observed in patients with

a CCI >0 when age was excluded from CCI calculation;

the significance remained high (beta = −0.16, P = 0.004)
when diabetes and serum albumin were added as adjustment
covariates.

Survival analysis

The mean follow-up was of 18.8 ± 6.7 months. During

the observational period, 77 out of 411 patients (18.8%) died:

31 (40.3%) and 46 (59.7%) because of cardiovascular
events and other causes, respectively. Figure 2 shows the
Table 2. Characteristics of incident chronic haemodialysis patients subdivided according to circulating iPTH levels

<table>
<thead>
<tr>
<th></th>
<th>iPTH &lt; 150 pg/ml</th>
<th>iPTH 150–300 pg/ml</th>
<th>iPTH &gt; 300 pg/ml</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>132 (32.1)</td>
<td>126 (30.7)</td>
<td>153 (37.2)</td>
<td></td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>62.9</td>
<td>69.0</td>
<td>58.8</td>
<td>N.S.</td>
</tr>
<tr>
<td>Age: median (range)</td>
<td>68.0 (22–90)</td>
<td>70.5 (23–92)</td>
<td>69.0 (21–96)</td>
<td>N.S.</td>
</tr>
<tr>
<td>CCI: median (range)</td>
<td>4.0 (0–14)</td>
<td>5.0 (0–13)</td>
<td>4.0 (0–15)</td>
<td>N.S.</td>
</tr>
<tr>
<td>CCI excluding age: median (range)</td>
<td>2 (0–10)</td>
<td>2 (0–10)</td>
<td>1 (0–11)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetic patients (%)</td>
<td>26.5</td>
<td>28.6</td>
<td>16.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypertensive patients (%)</td>
<td>53.8</td>
<td>56.5</td>
<td>65.5</td>
<td>N.S.</td>
</tr>
<tr>
<td>Hypotensive patients (%)</td>
<td>0.8</td>
<td>0.9</td>
<td>1.4</td>
<td>N.S.</td>
</tr>
<tr>
<td>Late referred patients (%)</td>
<td>45.5</td>
<td>33.5</td>
<td>27.5</td>
<td>0.005</td>
</tr>
<tr>
<td>Cigarette smoking (%)</td>
<td>29.7</td>
<td>24.6</td>
<td>20.5</td>
<td>N.S.</td>
</tr>
<tr>
<td>Haemoglobin &lt; 11 g/dl (%)</td>
<td>78.6</td>
<td>75.4</td>
<td>71.9</td>
<td>N.S.</td>
</tr>
<tr>
<td>C-rp = 3.11 mg/dl (%)</td>
<td>40.2</td>
<td>34.0</td>
<td>32.4</td>
<td>N.S.</td>
</tr>
<tr>
<td>Serum albumin = 3.2 g/dl (%)</td>
<td>34.4</td>
<td>22.4</td>
<td>23.9</td>
<td>N.S.</td>
</tr>
<tr>
<td>Corrected calcium &gt; 9.5 mg/dl (%)</td>
<td>44.8</td>
<td>38.3</td>
<td>27.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Corrected calcium &lt; 8.4 mg/dl (%)</td>
<td>6.4</td>
<td>13.9</td>
<td>21.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Phosphorus &gt; 5.5 mg/dl (%)</td>
<td>32.1</td>
<td>42.9</td>
<td>43.8</td>
<td>N.S.</td>
</tr>
<tr>
<td>Phosphorus &lt; 3.5 mg/dl (%)</td>
<td>17.6</td>
<td>7.9</td>
<td>9.2</td>
<td>0.02</td>
</tr>
<tr>
<td>All active vitamin D administration (%)</td>
<td>25.0</td>
<td>35.7</td>
<td>48.0</td>
<td>0.0003</td>
</tr>
<tr>
<td>Oral calcitriol administration (%)</td>
<td>22.7</td>
<td>29.4</td>
<td>27.7</td>
<td>N.S.</td>
</tr>
<tr>
<td>Phosphate binders administration (%)</td>
<td>67.4</td>
<td>76.0</td>
<td>73.9</td>
<td>N.S.</td>
</tr>
<tr>
<td>Calcium salts administration (%)</td>
<td>40.2</td>
<td>44.0</td>
<td>52.9</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

C-rp 3.11 mg/dl = third tertile; serum albumin 3.2 g/dl = first quartile; haemoglobin, iPTH, calcium and phosphate concentrations are categorized according to K/DOQI recommendations for stage 5 CKD.

Table 3. Clinical and laboratory characteristics (mean ± standard deviation) of incident chronic haemodialysis patients subdivided according to circulating iPTH levels

<table>
<thead>
<tr>
<th></th>
<th>iPTH &lt; 150 pg/ml (mean ± SD)</th>
<th>iPTH 150–300 pg/ml (mean ± SD)</th>
<th>iPTH &gt; 300 pg/ml (mean ± SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.1 ± 13.4</td>
<td>66.5 ± 15.9</td>
<td>66.8 ± 15.0</td>
<td>N.S.</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>144 ± 22</td>
<td>144 ± 23</td>
<td>142 ± 24</td>
<td>N.S.</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>77 ± 11</td>
<td>80 ± 12</td>
<td>78 ± 12</td>
<td>N.S.</td>
</tr>
<tr>
<td>Corrected calcium (mg/dl)</td>
<td>9.43 ± 0.85</td>
<td>9.27 ± 0.80</td>
<td>9.06 ± 0.86</td>
<td>0.003</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>4.91 ± 1.53</td>
<td>5.32 ± 1.62</td>
<td>5.36 ± 1.46</td>
<td>0.01</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>9.72 ± 1.39</td>
<td>9.96 ± 1.53</td>
<td>10.1 ± 1.39</td>
<td>N.S.</td>
</tr>
<tr>
<td>C-rp (mg/dl)</td>
<td>4.80 ± 6.81</td>
<td>3.95 ± 6.27</td>
<td>3.64 ± 6.40</td>
<td>N.S.</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>3.38 ± 0.57</td>
<td>3.55 ± 0.52</td>
<td>3.60 ± 0.54</td>
<td>0.02</td>
</tr>
</tbody>
</table>

CCI-adjusted (CCI as continuous variable) relative risk of death for all-cause, non-cardiovascular and cardiovascular causes, grouping patients on iPTH concentration and assuming iPTH = 150–300 pg/ml as reference. The relative risk of death increased in patients with iPTH <150 pg/ml, but reached the statistical significance only for all-cause mortality.

The Kaplan–Meier survival curves for all-cause mortality (Figure 3) point out a significantly (P < 0.00001) worse survival for patients with a combination of highest tertile of CCI and lowest one of iPTH.

The results of multivariable-adjusted Cox analysis to test the effect on survival of several combinations between tertiles of CCI and tertiles of iPTH are shown in Figure 4. The worst combination for all-cause mortality was second and third tertiles of CCI with first tertile of iPTH (RR = 3.83, P = 0.02; RR = 3.79, P = 0.01, respectively). Finally, the interaction between iPTH and CCI on patient survival was underlined in the interaction test where the interaction term iPTH × CCI was significantly associated with all-cause mortality (beta = −0.20, P < 0.05).

Discussion

The increased serum concentration of phosphate and calcium has adverse effects on survival of patients on chronic
RRT [17–20]. PTH has been often associated with higher mortality rate [17–20]. Instead, survival analyses have yielded conflicting results on the effects of low PTH [17–23].

The incident dialysis population represents an interesting cohort to identify potential causes of high mortality observed within the first year of dialysis. In this population, both high and low PTH were correlated with a significant reduction in the quality of life, while low PTH had no detrimental effect on survival [20,24].

In the present study, we have evaluated the data of 411 incident haemodialysis patients and found a very high overall rate of clinical complications.

Late referral and low concentration of serum albumin were frequently found in patients with low iPTH; the latter finding may indicate sub-optimal clinical care of patients in pre-dialysis stages and consequent malnutrition.

An inverse relationship between the CCI and iPTH was observed in comorbid patients, and it was independent of diabetes, active vitamin D administration and concentrations of serum calcium, phosphate and albumin. Potential links between the CCI and iPTH may be the limitation in skeletal mobilization and/or the malnutrition frequently observed in patients with high-grade comorbidities. In fact, the limitation in skeletal mobilization may increase serum calcium with consequent reduced secretion of iPTH. Despite the fact that high serum calcium and low serum albumin were more frequently found in our patients with low iPTH, the inverse association between the CCI and iPTH was independent of both variables. However, it is difficult to deduce from PTH levels the metabolic state of bone. Not all patients with low iPTH have reduced bone turnover; at the same time, patients with high iPTH do not have increased turnover [25].

The lack of an increased risk of death in patients with iPTH > 300 pg/ml should be viewed with caution because only 9% of the entire cohort had iPTH > 600 pg/ml which has been associated with an increased mortality in prevalent dialysis patients [18]. The weak statistical association between low iPTH and CCI-adjusted risk of death and the presence of inverse correlation between iPTH and CCI prompted us to look for more distinctive interactions between both factors and evaluate the impact of their combinations on all-cause mortality. The attained data highlighted the hazardousness of the combinations of lowest tertile of iPTH and highest tertiles of the CCI. Remarkably, the detrimental effect of high CCI on survival was mostly evident in patients with low iPTH. However, a trend between rising CCI and risk of death was observed also in patients with high tertiles of iPTH; the lack of statistical significance may be due once more to the low percentage of patients with very high iPTH.

From the standpoint of the clinical implications, more attention should be devoted to all interventions aiming at attenuating the high mortality risk present in haemodialysis patients.
patients with low iPTH and high CCI. The first step is a better management of the alterations in mineral metabolism, an aspect that showed some inadequacies. In fact, at the start of RRT vitamin D and calcium salts were still administered to 25.0% and to 40.2% of our patients with a low concentration of serum iPTH, respectively. Despite observational studies which have shown a beneficial effect of vitamin D compounds on patients’ survival, in our patients the detrimental effect of low iPTH and high CCI on survival was independent of vitamin D administration, at least at the start of RRT.

The present study has some limitations. iPTH was obtained at several renal units with different second generation assay methods. Nonetheless, the regression model multilevel analyses did not show any significant influence of the nested levels method and centre. Survival analysis based on a single baseline value of iPTH may be questioned, but this is the case of many other studies. Furthermore, the mortality risk was not different when iPTH was analysed at baseline, as a standard time-dependent covariate and as a cumulative time-dependent covariate [24]. Data analysis took into account only drugs administered at the start of RRT but not the variations occurring during the observation period. In some patients the follow-up might appear too short, but only 5% and 1% of patients had censoring time shorter than 12 and 6 months, respectively. Of note, these patients were free from events; their influence on the outcome analysis may be regarded as negligible.

In conclusion, incident haemodialysis patients suffer from a high rate of clinical complications. In these patients, low iPTH and high CCI are often associated and their interaction affects survival negatively.

Conflicts of interest statement. None declared.

Appendix: investigators of the CPCP (Comorbidity—Parathormone—Calcium—Phosphate) study

Paolo Altieri Azienda Ospedaliera Brotzu—CAGLIARI; Enzo Ancarani, Ospedale Belcolle ASL—VITERBO; Fabrizio Assini, Ambulatorio Emodialisi San Pio—AFRAGOLA (NA); Alice Atzeni, Unità Ospedaliera Dialisi Territoriale—CAGLIARI; Maria Auricchio, Presidio Ospedaliero San Leonardo—CASTELLAMARE DI STABIA (NA); Guido Bellinghieri, Università degli Studi di Messina—MESSINA; Piergiorgio Bolasco, Unità Ospedaliera Dialisi Territoriale—CAGLIARI; Francesco Bondatti, Ospedale S. Benedetto—ALATRI (FR); Diego Brancaccio, Azienda Ospedaliera San Paolo Polo Universitario—MILANO; Maurizio Brigante, Azienda Ospedaliera Cardarelli—CAMPOBASSO; Maria Capuano, Ospedale dei Pellegrini—NAPOLE; Maria Cesarano, Presidio Ospedaliero San Leonardo—CASTELLAMARE DI STABIA (NA); Stefano Chimenti, Ospedale Civile Giannuzzi—MANDURIA (TA); Pasquale Coratelli, Azienda Università Ospedaliera Policlinico—BARI; Roberto Corciulo, Azienda Università Ospedaliera Policlinico—BARI; Alex Corsaro, Azienda Ospedaliera Istituti Ospitalieri—VERONA; Olga Credentino, Azienda Ospedaliera Cardarelli—NAPOLE; Ludovica D’apice, Azienda Ospedaliera S. Sebastiano—CASERTA; Filomena D’elia, Presidio Ospedaliero—MOLFETTA (BA); Teresa Dipalma, Azienda Università Ospedaliero Istituti Ospitalieri—VERONA; Biagio Raffaele Di Iorio, Ospedale Landolfi—SOLOFRA (AV); Silvio Di Stante, Azienda Ospedaliera Cardarelli—CAMPOBASSO; Raffaela Esposito, Ambulatorio Emodialisi San Biagio—CASORIA (NA); Riziero Fini, Ospedale S. Benedetto—ALATRI (FR); Antonio Galise, Ambulatorio Emodialisi C.M.M.—CAVA DEI TIRRENI (NA); Loreto Gesualdo, Azienda Università Ospedaliera Ospedali Riuniti—FOGGIA; Antonio Gesueto, IRCCS Casa Sollievo della Sofferenza—S. GIOVANNI ROTONDO (FG); Pasqua Giangregorio, Presidio Ospedaliero—MOLFETTA (BA); Michele Gian-nattasio, Ospedale S.Maria degli Angeli—PUTIGNANO (BA); Giuseppina Giannetto, Azienda Ospedaliera Gravina—CALTAGIRONE (CT); Francesco Godino, Presidio Ospedaliero SS Annunziata—TARANTO; Emilio Iele, Azienda Ospedaliera Rummo—BENEVENTO; Maria Ktena, Azienda Università Ospedaliera Ospedali Riuniti—FOGGIA; Graziella Leotta, Azienda Ospedaliera Gravina—CALTAGIRONE (CT); Cosimo Lodesterto, Presidio Ospedaliero SS Annunziata—TARANTO; Antonio Lupo, Azienda Ospedaliera Istituti Ospitalieri—VERONA; Vilma Martella, Azienda Università Ospedaliera Policlinico—BARI; Carlo Massimetti, Ospedale Belcolle ASL—VITERBO; Mario Migliorati, Ambulatorio Emodialisi San Giorgio—TORRE DEL GRECO (NA); Fernanda Misceo, Centro di Emodialisi New Dial—BARI; Nicola Mongelli, Centro Dialisi Ambulatoriale C.B.H.—BISCEGLIE (BA); Ilaria Napoletano, Ospedale San Giovanni Decollato Androsilla—CIVITA CASTELLANA (VT); Donato Paoletti, Presidio Ospedaliero Lastaria—LUCERA (FG); Sergio Papagni, Centro Dialisi Ambulatoriale C.B.H.—BISCEGLIE (BA); Giovanni Maria Passaghe, Presidio Ospedaliero Dettori—TEMPIO PAUSANIA (SS); Silvia Porreca, Azienda Università Ospedaliera Policlinico—BARI; Paolo Rampa, Ospedale Civile Spirito Santo—PESCARA; Pietro Ravani, Azienda Ospedaliera Istituti Ospitalieri—CREMONA; Paolo Riveruzzi, Ospedale San Giovanni Decollato Androsilla—CIVITA CASTELLANA (VT); Roberto Russo, Azienda Università Ospedaliera Policlinico—BARI; Antonio Santoro, Policlinico Sant’Orsola Malpighi—BOLOGNA; Antonio Sarti, Presidio Ospedaliero—SCAFATI (SA); Caterina Saviano, Azienda Ospedaliera S. Sebastiano—CASERTA; Vincenzo Savica, Università degli Studi di Messina—MESSINA; Antonio Savino, Ambulatorio Emodialisi Capodichino—NAPOLE; Francesco Paolo Schena, Azienda Università Ospedaliera Policlinico—BARI; Palmira Schiavone, AUSL BR/1 Presidio Ospedaliero “A. Perrino”—BRINDISI; Carmine Stallone, IRCCS Casa Sollievo della Sofferenza—S. GIOVANNI ROTONDO (FG); Davide Stallato, Azienda Ospedaliera Rummo—BENEVENTO; Paolo Strippoli, AUSL BR/1 Presidio Ospedaliero “A. Perrino”—BRINDISI; Vincenzo Tedesco, Presidio Ospedaliero—SCAFATI (SA); Giuseppe Tomasio, Ambulatorio Emodialisi San Giorgio—TORRE DEL GRECO (NA); Serena Torraca, Ambulatorio Emodialisi C.M.M.—CAVA DEI TIRRENI (NA).
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