Although peritoneal dialysis (PD) has been recommended for initial dialysis therapy, a larger proportion of patients with end-stage renal disease choose hemodialysis (HD) instead. Several previous studies comparing the outcomes of these two therapies, including survival rates and cardiovascular events, have not clearly demonstrated the superiority of one over the other. Our recent study indicated that, compared with HD or PD alone, renal replacement therapy with HD and PD in combination prolongs survival and reduces cardiovascular events. However, the use of combination dialysis therapy is not widely accepted. We set out to analyze the efficacy of combination dialysis therapy with PD and HD in patients who started with PD as initial dialysis therapy.

Our single-center retrospective cohort study included 401 patients (165 women, 236 men; 61 ± 12 and 62 ± 9 years of age respectively) who started PD during 1995 – 2005. Chart and electronic databases were used to obtain information on the course of dialysis therapy, including mortality and cardiovascular events.

Treatment with HD and PD in combination was used in 103 patients. During 5 years of follow-up after the start of PD, 80 patients died. We observed no differences in cumulative mortality between the men (49, 20%) and women (31, 18%) and no difference in the cumulative incidence of catheter removal for various reasons (35% vs. 31%). There was a significant difference ($p < 0.05$) in the time of HD start between men and women. In men on PD, HD therapy was started $22 ± 2$ months after the start of PD; in women, it was started $38 ± 7$ months after PD start.

Although women have a survival advantage in both the general and the dialysis patient population, women on PD experience mortality similar to that in men. The reasons for those findings have not been fully explained. The present analysis suggests that an early start to HD therapy will prolong the survival of patients on PD, especially men.

Key words Survival, gender, cardiovascular events, combination therapy

Introduction
In the general population, women are known to have a longer life expectancy than men. The difference might be partly explained by the lower prevalence of cardiovascular risk factors and events in women, who have also been found to have a longer life expectancy in populations in which atherosclerosis is a known health issue (1–4). However, several observational studies have reported that, unlike women in the general population, those on dialysis lose the survival advantage (5,6), and the mortality of men and women on dialysis is about the same. Carrero et al. (7) reported that in 1577 patients (61% men, 60 ± 5 years in age), both sexes presented equal survival in spite of a lower prevalence of cardiovascular disease in women. Those authors also found that the mortality risk was strikingly higher in diabetic women than in men, explaining the loss of survival
advantage for the women. They also mentioned a difference between peritoneal dialysis (PD) and hemodialysis (HD) patients, but no precise data were presented.

It remains to be established whether PD is good for diabetic patients (8), and physicians hesitate to select PD for them. Thus, the question of PD negating the survival advantage for women persists. Moreover, the most recent reports from Japan indicate that 18% of PD patients are being treated with a combination of PD and HD (9). In our center, the use of combined therapy with PD and HD is higher than the use of PD alone, especially for men.

Although PD is a better option than in-center HD for new patients starting renal replacement therapy (RRT), the rate of PD initiation in Japan has been declining. Masakene et al. (9) provided some possible explanations: the trauma of encapsulating peritoneal sclerosis, lesser experience with PD patients among younger nephrologists and nurses, and marked technologic developments in HD, among others. Issues of lower solute clearance and ultrafiltration in PD have remained unresolved despite improvements in various aspects such as dialysates, PD cyclers, and so on (10). To compensate for those problems, the combination of PD and HD has been introduced into clinical practice (11–15).

The aim of the present study was to test the hypothesis that an increase in the use of combination therapy in men would result in the same level of mortality as for women on PD. To that end, we analyzed the 5-year survival data for male and female PD patients at our center.

**Methods**

Our single-center retrospective cohort study included 401 patients (165 women, 236 men; 61 ± 12 and 62 ± 9 years of age respectively) who started PD as their initial dialysis treatment during 1995 – 2005. All patients were regularly monitored at our center and had started their PD treatment at least 6 months before enrollment.

Baseline data were collected on the demographic characteristics of the patients and on their laboratory values, PD prescription, and duration on dialysis before enrollment. Informed consent was obtained, and the trial was performed in accordance with the principles of the World Medical Association Declaration of Helsinki.

**Regular treatment modality at the Kidney Center of Saitama Medical University**

More than 60% of patients were practicing a standard continuous ambulatory peritoneal dialysis (CAPD) regimen with 4 daily 1.5-L or 2-L exchanges of dialysate; other patients used 2 – 3 daily exchanges. The concentration of the bags was individualized to maintain the desired weight. Dwell times were also individualized to maximize overall ultrafiltration volumes. During the study, all subjects were asked to maintain their customary dietary and dialysis regimens. Mean daily dietary intake was recorded from individual 24-hour food records during a 3-day period at the start of the study. All subjects consumed between 0.8 g and 1.0 g protein per kilogram body weight daily, and their energy intake exceeded 25 kcal/kg daily. Salt intake was restricted to less than 9 g daily.

A 4-hour HD session was added once weekly after 6 consecutive days of PD. On the morning of the HD session, before the session started, the PD dialysate was drained. A bicarbonate dialysate and a dialyzer with a polysulfone dialysis membrane was used for the HD session (duration: 3.5 hours).

Indices of the adequacy of dialysis, including weekly creatinine clearance, were calculated using the PD Adequest computer program for Windows (version 2.0: Baxter Healthcare, Tokyo, Japan). Creatinine clearance by HD was calculated using this formula:

$$\text{Creatinine clearance by HD} = \frac{\text{creatinine concentration} \times (\text{dialysate flow} \times \text{duration of dialysis} + \text{fluid removed})}{\text{dual volume}}$$

Creatinine clearance by HD was found to be 2000 – 2400 mg.

Patients underwent a standard monthly assessment of biochemical and hematologic indices. Data on pre- and post-HD blood pressure, use of antihypertensive medications, dose of epoetin and response, calcium and phosphate control, and hyperparathyroidism were recorded. If a subject’s systolic blood pressure exceeded 140 mmHg or the diastolic blood pressure exceeded 90 mmHg, antihypertensive therapy was initiated. The selection of antihypertensive agents depended on physician preference.

During the study period, subjects were treated with recombinant human erythropoietin as necessary, and their hemoglobin levels were maintained between 10 g/dL and 11 g/dL. Subjects were given
oral iron supplementation if they were diagnosed with iron deficiency.

Subjects with parathyroid hormone levels greater than 200 pg/mL were treated with 1,25(OH)2D3 and CaCO3 supplements; patients with levels lower than 70 pg/mL were treated with CaCO3 to reduce their degree of hyperphosphatemia. Doses were adjusted based on serum levels of calcium and phosphate. Lipid-lowering drugs, primarily statin derivatives, were administered if serum cholesterol levels exceeded 240 mg/dL.

Survival was defined as the number of days from baseline (3 months after the start of dialysis treatment) to the date of death; to censoring because of loss to follow-up (kidney transplantation or transfer to a nonparticipating dialysis center); to the end of follow-up at 1 January 2007; or to a maximum 5 years’ follow-up.

**Statistical analysis**

Results are expressed as mean ± standard error of the mean. Statistical analyses were performed using the Student t-test for unpaired samples and the Mann–Whitney test for comparison of means. Cumulative event-free curves were determined by Kaplan–Meier analysis, and the differences between the curves were analyzed using the log-rank test. Statistical significance was set at $p < 0.05$. All calculations were performed using the StatView statistical software package (version 5.0: SAS Institute, Cary, NC, U.S.A.).

**Results**

**Baseline characteristics**
Table I shows the baseline demographics of the full cohort of 401 patients. No significant differences were observed in the age and prevalence of kidney diseases in the patients.

**Survival during follow-up**
Of the 401 patients, 80 patients died (49 men, 31 women; Figure 1). Table II shows the causes of death; we observed no differences between men and women. The survival curves in Figure 1 also show no differences between men and women.

**Combination of HD and CAPD**
During the follow-up period, 73 men and 30 women started with HD as complementary dialysis therapy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>236</td>
<td>165</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>62±9</td>
<td>61±12</td>
</tr>
<tr>
<td>Primary kidney disease ($n$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>62</td>
<td>39</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>124</td>
<td>84</td>
</tr>
<tr>
<td>Renal vascular disease</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>5</td>
<td>13</td>
</tr>
</tbody>
</table>

![Figure 1](https://via.placeholder.com/150)

**Figure 1** Kaplan–Meier curves for cumulative survival in women (open circles) and men (open squares) for 5 years after the start of peritoneal dialysis. No difference in the survival rate was found between women and men.

**Table II** Causes of death in the study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths ($n$)</td>
<td>49</td>
<td>31</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Infection</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Table III shows the baseline characteristics for those patients. The reasons that HD was needed as combination therapy were insufficient solute removal (37 men, 11 women), insufficient ultrafiltration (20 men, 9 women), and both (16 men, 10 women). We
observed no differences between the causes for initiation of combination therapy, but men were started on combination therapy earlier than women were \((p < 0.05, \text{Figure 2})\).

**Catheter removal during follow-up**

During follow-up, catheters were removed for various reasons. Figure 3 presents a Kaplan–Meir curve for catheter removal. We observed no differences between men and women. Patients whose PD catheters were removed for any reason were eligible for the study. The decision to remove the PD catheter was made for these reasons: change from PD to HD; abdominal surgery, including resection of neoplasm; recurrent or relapsing peritonitis; peritonitis because of infection with *Pseudomonas*, tuberculosis, or *Candida*; and transplantation.

**Discussion**

In the present study, we found no significant differences in 5-year survival between men and women on PD. During the 5-year follow-up, the average age of patients who died was greater than that of patients who survived. The number of patients treated with combination therapy was significantly higher among the men than the women. In addition, combination therapy was initiated significantly earlier in men than in women.

Recently, based on the NECOSAD (Netherlands Cooperative Study on the Adequacy of Dialysis) prospective observational cohort, Carrero *et al.* (7) reported that women starting dialysis had the same mortality risk as men despite having a cardiovascular disease comorbidity at baseline that was lower by a factor of nearly 2. The findings by those authors accord with those reported in previous publications (5,6,16). Carrero *et al.* speculated that differences in body mass index or dialysis care could explain the findings. In addition, women were more likely than men to have diabetes. A previous report supported the explanation, having showed that among end-stage renal disease patients with type 2 diabetes who were more than 65 years of age, women had a slightly greater mortality risk than did men. In our

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients ((n))</td>
<td>73</td>
<td>30</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>55±11</td>
<td>53±12</td>
</tr>
<tr>
<td>Primary kidney disease ((n))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
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<tr>
<td>Renal vascular disease</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>
study, although the proportion of diabetic patients was higher among women than among men, the difference was not significant. An alternative explanation for the survival differences may be that they reflect different responses to dialysis therapy, including less-effective PD in patients of small body size (17).

Among the factors potentially leading to CAPD discontinuation, peritoneal transport status—which may be associated with adverse clinical outcomes (18)—is of utmost importance. Moreover, peritoneal transport status and weekly creatinine clearance have been demonstrated to be associated (19,20). Guideline targets for solute clearance have now emerged, the most prominent being that issued by the U.S. National Kidney Foundation in its Kidney Disease Outcomes Quality Initiative (21). The guideline stipulates a weekly creatinine clearance of more than 60 L per 1.73 m² body surface area. To achieve an adequate weekly creatinine clearance, several methods are suggested. One is the use of automated PD, although no decisive data have been generated to demonstrate the effects of increasing such prescriptions on patients’ outcomes. Because a single HD session is equivalent to 2 – 3 days of CAPD in terms of creatinine clearance, the addition of HD for CAPD patients who do not achieve weekly creatinine clearance targets is a possible alternative strategy (11,22).

In addition, our study demonstrated that more men than women underwent combination therapy with PD and HD. It is well known that patients on PD therapy frequently experience deficient solute removal. Previously, and in agreement with other recent publications (11–15), our studies (23,24) clearly demonstrated that combination therapy improves the deficiency in solute removal and increases serum albumin and hemoglobin concentrations. Those parameters are known indicators of nutrition status and contribute to survival in both HD and PD patients (25,26). In our cohort, not only was the rate of combination therapy higher in men than in women, but men on PD were started on combination therapy significantly earlier than women were. The findings of the present study suggest that the use of combination therapy and an earlier start to that use may prolong survival in men on PD.

Certain caveats accompany the interpretation of the present study. It cannot be denied that the number of patients studied is smaller than in other recent publications (5–7,16). In addition, the burden of cardiovascular disease was not evaluated before initiation of PD therapy, and the interaction of baseline cardiovascular risk factors with 5-year mortality in end-stage renal disease patients is well known (27). The impact of this selection bias on the survival difference between the men and the women is not known. Furthermore, no precise target level of dialysis adequacy was determined in our observational study.

Conclusions
The present study shows that combination therapy with HD and PD might be helpful in prolonging survival. Moreover, an earlier start to complementary HD was helpful in prolonging survival, particularly in men.

Disclosures
The authors have no financial conflicts of interest to declare.

References

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