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Treatment and clinical outcomes of elderly idiopathic membranous nephropathy: A multicenter cohort study in Korea

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ABSTRACT

Idiopathic membranous nephropathy (MN) is the most common glomerulonephritis in elderly patients showing nephrotic syndrome. However, little is known about its treatment options and outcomes in elderly MN patients at long term follow-up. We retrospectively enrolled patients with biopsy-proven MN between April 1990 and December 2015 from eight tertiary hospitals in Korea. Among them, we excluded patients who had secondary causes of MN and subnephrotic-range proteinuria. We evaluated the presenting features and clinical outcomes and analyzed the all-cause mortality, renal outcomes, infection, and remission with respect to age. During the median follow-up at 77.2 months, 198 younger patients (< 65 years) and 133 elderly patients (≥65 years) were enrolled. Age was an independent risk factor for all-cause mortality, renal outcome, and infection (for all $P < 0.05$) except remission. In elderly patients, there was no significant factor associated with mortality rate. The use of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) was significantly associated with renal outcome and infection (renal outcome, hazard ration [HR] 0.06, 95% confidence intervals [CI] 0.01–0.36, $P = 0.003$; infection, HR 0.20, 95% CI 0.04–0.94, $P = 0.041$). Immunosuppressant therapy significantly increased renal outcome ($P = 0.045$) and infection ($P = 0.029$) compared with conservative therapy. In conclusion, old age is one of the clinically important predictors for MN patients. Among the treatment of elderly MN patients, only ACEI or ARB was associated with beneficial effects on renal outcome and infection. Elderly MN patients need a more tailored regimen considering their comorbidities and condition.

1. Introduction

The world population continues to rapidly grow older and life expectancies have increased (Tonelli & Riella, 2014). Hence, the aging kidney has become a topic of great interest in geriatric medicine and clinical nephrology. With advancing age, various structural changes occur, including micro-anatomic changes, such as nephrosclerosis and a decline in nephron number, and macro-anatomic changes, such as decreased kidney cortical volume and the development of renal cysts (Glassock & Rule, 2012). Moreover, glomerular filtration rate (GFR) declines with age, which is correlated with structural changes (Weinstein & Anderson, 2010) and vascular processes (Cattran, 2005). Although elderly patients have the same GFR and amount of proteinuria compared with younger patients, their prognosis may be different.

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Idiopathic membranous nephropathy (MN) is one of the common histologic findings in adult glomerulonephritis (Davison & Johnston, 1996; Jin et al., 2014; Prakash, Singh, & Saxena, 2003; Shin et al., 2001), especially in elderly nephrotic syndrome (Davison & Johnston, 1996). Idiopathic MN is a well-known autoimmune disease; antibodies against glomerular antigens, phospholipase A2 receptor 1, and thrombospondin type-1 domain-containing 7A, have recently been revealed as causes (Tomas et al., 2014). Therefore, immunosuppressive therapy combined with steroids are effective for inducing remission and reducing renal progression (Cattran et al., 2012; du Buf-Vereijken, Branten, & Wetzels, 2004; Howman et al., 2013).

Although the incidence of MN is higher in the elderly than in young adults (Cameron, 1996; Yokoyama et al., 2012), studies of immunosuppressive therapy in elderly MN patients are scarce. The risks of immunosuppressive agents increase in the elderly (Cattran et al., 2012). The elderly population is already in an immunosuppressed state due to declining age-related immune function, and this results in the development of cancer and infectious, and chronic inflammatory diseases (Fulop et al., 2007; Vasto, Malavolta, & Pawelec, 2006). Furthermore, immunosuppressive therapies worsen comorbid diseases, such as cardiovascular diseases, diabetes, and metabolic syndrome (Wong & Koo, 2012). Consequently, additional studies on the optimal therapeutic choice for elderly MN patients are needed.

In this study, we investigated the clinical features and treatment pattern of idiopathic MN in the elderly population, and compared them with those of the younger idiopathic MN patients in a Korean multicenter cohort.

2. Materials and methods

2.1. Study subjects and clinical data collection

This was a multi-center, retrospective cohort study. We enrolled patients with biopsy-proven idiopathic MN between April 1990 and December 2015 from eight tertiary hospitals in Korea. Among them, we excluded patients who had subnephrotic range proteinuria and had secondary causes of the MN, such as an autoimmune disease, neoplasia, infection, or drugs (Fig. 1).

Data on baseline demographic and clinical characteristics were obtained from a review of the medical records. Baseline information included age, sex, height, weight, serum hemoglobin, albumin, cholesterol, serum creatinine, 24-h urinary protein excretion, urinary protein-to-creatinine ratio (UPCR), and comorbid diseases. Body mass index (BMI) was calculated as weight in kg ÷ (height in m)^2 and the estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation (MDRD). We gathered information about medications, including angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blocker (ARBs), calcium channel blockers (CCBs), diuretics, lipid lowering agents, and immunosuppressants. The study was approved by the institutional review boards of each center.

2.2. Definitions

Nephrotic syndrome was defined as the presence of generalized edema, heavy proteinuria of > 3.5 g/d, hypoalbuminemia < 3.5 g/dl, and/or hypercholesterolemia. Complete remission (CR) was defined as the absence of proteinuria (UPCR < 0.3 g/g cr), confirmed by two values at least 1 week apart, accompanied by a normal serum albumin concentration and a normal serum creatinine (Yamaguchi et al., 2014). Partial Remission was defined as a urinary protein excretion of < 3.5 g/d and a 50% or greater reduction from peak values; confirmed by two values at least 1 week apart.

2.3. Clinical outcomes

For the primary analysis, data on the all-cause mortality, hospitalization due to infection, renal outcome, and remission were collected. We defined renal outcomes as composite of doubling of serum creatinine or progression to ESRD.

2.4. Statistical analysis

To compare the baseline characteristics according to age, patients were stratified into two groups: < 65 years and ≥65 years. Differences among the age groups were tested using the χ^2 test for categorical variables, and the analysis of variance *t*-test for continuous variables. To explore the association between the age and clinical outcome in MN patients, a Kaplan-Meier curve was plotted according to the two age groups. Survival differences were compared by the log-rank test. To calculate the relative risk of death, hazard ratios (HRs) and 95% confidence intervals (CI) were obtained using Cox proportional hazards models. Factors that showed a significant association ($P < 0.05$) after univariate analysis or were of important clinical concern were entered into the multivariate Cox regression analysis. Variable selections were performed using backward elimination, forward stepwise selection

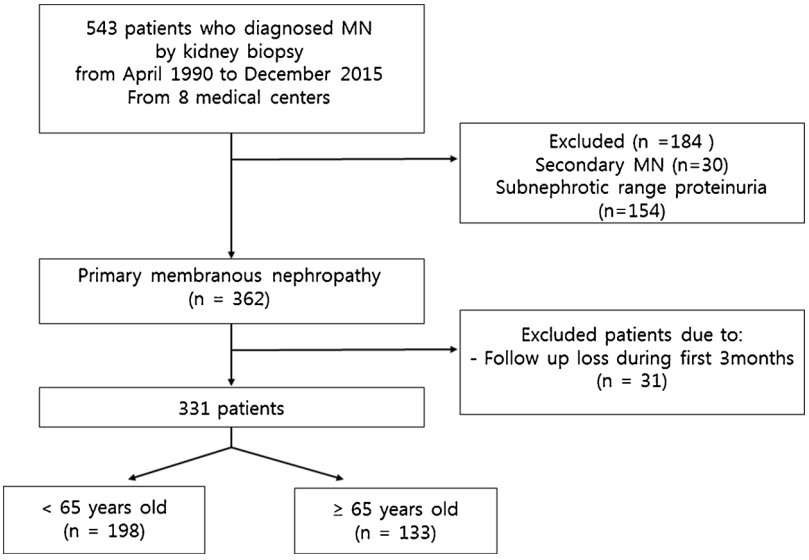

Fig. 1. Flow chart of study enrollment.