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Original Article

Prognostic factors and survivals of children with steroid-resistant nephrotic syndrome

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Abstract

Background Children with steroid resistant nephrotic syndrome (SRNS) generally survive, although during the course of disease their kidney function may decrease, leading to end-stage renal disease (ESRD). There have been few studies reporting on the survivals of children with SRNS.

Objectives To determine patient and kidney survival rates in children with SRNS at the first, second, third, fourth, and fifth years; and to evaluate the effects of age at onset, initial kidney function, hypertension, and type of resistance, on the survivals of children with SRNS.

Methods This retrospective cohort study was performed using secondary data obtained from medical records of patients with SRNS in Department of Child Health, Cipto Mangunkusumo Hospital, between 2004-2011. The outcomes of kidney survivals were defined in two ways: lack of doubling of base creatinine levels and lack of ESRD.

Results There were 45 children with SRNS in our study. Their median duration of illness was 24 (range 12-95) months. Twenty percent of the subjects died, 31.1% had a doubling of base creatinine levels, and 13.4% developed ESRD. Life survival rates of subjects at the first, second, third, fourth, and fifth years after diagnosis were 93%, 84%, 80%, 72% ,and 61%, respectively. Kidney survival rates determined by the lack of doubling of base creatinine levels at the first, second, third, fourth and fifth years were 92%, 72%, 56%, 42%, and 34%, respectively, while kidney survival rates determined by the lack of ESRD were 97%, 88%, 81%, 70%, and 58%, respectively. Age at onset, initial kidney function, hypertension at onset, and type of resistance, did not significantly affect the survivals of children with SRNS.

Conclusion Children with SRNS are prone to develop a doubling of base creatinine levels and ESRD. Factors such as age, initial kidney function, hypertension at onset, and type of resistance, do not significantly affect both, life and kidney survivals of children with SRNS. **[Paediatr Indones. 2013;53:42-9.]**

Keywords: *steroid-resistant nephrotic syndrome, end-stage renal disease, doubling of base creatinine levels, survival*

Nephrotic syndrome (NS) is the most common manifestation of glomerulopathy in children.[1,2] Based on patient response to steroid treatment, NS is divided into two types: steroid-sensitive nephrotic syndrome (SSNS) and steroid-resistant nephrotic syndrome (SRNS). Steroid resistance nephrotic syndrome is reportedly seldom in children, comprises only 10-20% of NS cases, and was found in approximately 15.4% of NS cases in Cipto Mangunkusumo Hospital, Jakarta.[3-6] Children with SRNS generally have good survival rates, although during the course of the disease they may develop decreased kidney function, leading to a condition where the kidney function is not compatible with life, called end-stage renal disease (ESRD). In children with SRNS, the risk of progression to ESRD is high, reaching approximately 50%.[7,8] Previous studies have shown a 15-year survival rate of 97%, whereas kidney survival was approximately 53%.[7] There has been little data on the survival of children with SRNS published in Indonesia.

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We aimed to determine the life and kidney survival rates of children with SRNS at the first, second, third, fourth and fifth years after onset. We also assessed the effects of several potential prognostic factors for survival, such as age at onset, initial kidney function, hypertension at onset, and type of resistance, in children with SRNS. Data on survival rates may help us better manage SRNS patients, educate patients on prognosis, and also provide a basis for further study.

Methods

A retrospective cohort study was performed using secondary data obtained from medical records of SRNS patients registered in Department of Child Health, Cipto Mangunkusumo Hospital, between January 2004-January 2011. We included all children diagnosed with SRNS, aged 1-18 years at the time of diagnosis, who had been diagnosed for at least 12 months. Patients with incomplete medical records were excluded. Dependent variables were event of death, as well as the occurence of a doubling of base creatinine levels and ESRD (defined as glomerular filtration rate $\leq$ 15 mL/min/1.73m^2). Independent variables were age at SRNS onset, initial kidney function, hypertension at onset, and type of resistance. Age at onset was divided into <10 and ≥10 years of age. Initial kidney function was divided into stages of chronic kidney disease. Stages of chronic kidney disease (CKD) from I-V were defined as glomerular filtration rates (calculated by Schwartz formula) of ≥ 90, 60-89, 30-59, 15-29, and ≤15 mL/min/1.73m^2 (or requiring routine dialysis), respectively. Hypertension was categorized as with or without hypertension at the time of onset. Type of resistance was defined as primary or secondary resistance.

The total sample size was estimated by multiplying the amount of independent variables with 5-50, resulting in 20-200 subjects needed. Patients who did not routinely visit the Pediatric Nephrology clinics had home visits to determine their survival status. Those with incomplete kidney function data had their kidney function evaluated. At the end of the study, patients were classified as having normal or decreased kidney function, died, or lost to follow-up (defined as patients whose status could not be determined until the end of the study period).

Kaplan-Meier curves were constructed for each of the outcomes, followed by bivariate analysis to identify any associations between the variables. Survival curves that fulfilled the proportional hazard assumption were analyzed by time-independent Cox regression analysis, while those that did not fulfill the requirement were analyzed by time-dependent Cox regression. Multivariate analysis was further performed for variables with a P value of <0.25. All statistical analyses were performed using the IBM-SPSS program version 19. This study was approved by the Ethics Commitee of the University of Indonesia Medical School. All patients and parents were given a complete explanation of the study. Subjects' parents provided written informed consents.

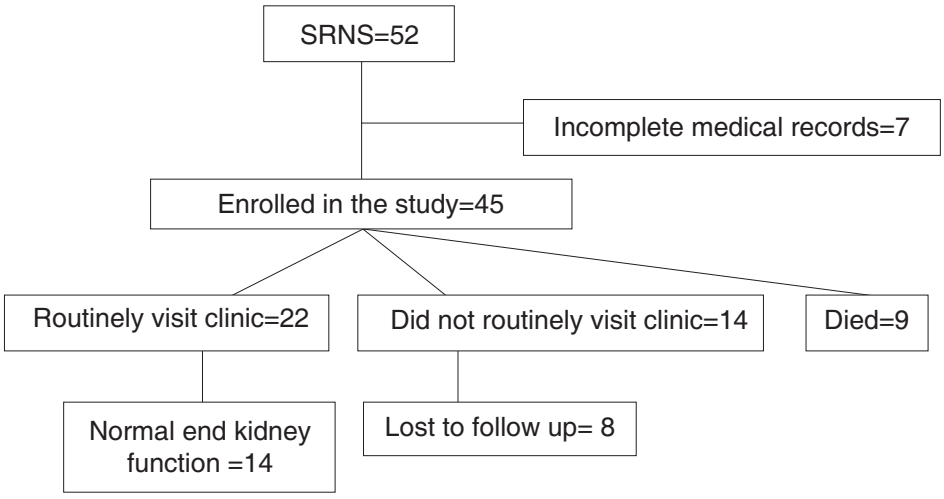

Figure 1. Flow chart of patients selection

Results

After searching the medical records between January 2004-January 2011 we found 52 patients with SRNS, 7 were excluded, and the other 14 did not routinely visit the Pediatric Nephrology clinics. Eight of the 45 included patients were considered lost to follow up (**Figure 1**), 9 children died, while 28 children were survived. Baseline characteristics of subjects are presented in **Table 1**.

Subjects' median age was 7.7 (range 2.5-16.4) years and 37 subjects (82.2%) were below the age of 10 years at SRNS onset. Subjects' median baseline creatinine level was 0.4 (range 0.1-2) mg/dL at onset, and was 0.7 (range 0.2-23.7) mg/dL at time of this study. At the onset of the disease most of patients (80%) were in stage I of CKD, while no patient was in stage IV-V **(Table 2).**

Life Survival Rates

Nine out of 45 patients (20%) died due to CKD. Sepsis and heart failure caused death in 7 patients, while the other two died of unknown causes. The overall 5-year survival of patients with SRNS was 61% (95%CI 34.7-86.4) (**Figure 2**). Survival was further described according to prognostic factors of initial kidney function, age at onset, type of resistance, and hypertension at time of onset.

The five-year survival of patients with initial CKD stages I, II, III were 70%, 0%, and 67%, respectively, with no significant difference between groups (P=0.495). Survival of patients with age at onset <10 years was 77%, compared to 19% in those with age of onset ≥ 10 years, although this difference also was not statistically significant (P=0.337). Primary and secondary steroid-resistant NS patients had survivals of 61% and 71%, respectively, but were not significantly different (P=0.344). The hypertensive group survival was 76% after 4 years, while that of the non-hypertensive group was 73% after 4 years and 62% after 5 years (P=0.319). Multivariate analysis could not be performed since not all variables fulfilled the proportional hazard assumption. In addition, there was no variables with P value <0.25.

Table 1. Baseline characteristics

Characteristics	n=45
Median duration of illness, months (range)	24 (12-95)
• Died, n=9	17 (12-50)
• Survived, n=28	24.5 (12-95)
Sex, n (%)	
• Male	28 (62.2)
• Female	17 (37.8)
Microscopic hematuria at onset, n (%)	17 (37.7)
Hypertension at onset, n (%)	18 (40)
Median increase in creatinine level (range), times	1.42 (0.83-107.14)
Median annual increase in creatinine (range), times/year	1.75 (0.18-22.13)
Type of resistance, n (%)	
• Primary SRNS	12 (26.7)
• Secondary SRNS	33 (73.3)

Table 2. Comparison of baseline characteristics at onset and at beginning of study

Characteristics	At onset	At the study time
Median age (range), years	5.1 (0.2-15.1)	7.7 (2.5-16.4)
Age by group, n (%)		
• < 10 years	37 (82.2)	30 (66.7)
• ≥ 10 years	8 (17.8)	15 (33.3)
Initial kidney function, n (%)		
• CKD stage I	36 (80)	23 (51.1)
• CKD stage II	6 (13.3)	7 (15.6)
• CKD stage III	3 (6.7)	7 (15.6)
• CKD stage IV	0	2 (4.4)
• CKD stage V	0	6 (13.3)
Median creatinine level (range), mg/dL	0.4 (0.1-2)	0.7 (0.2-23.7)

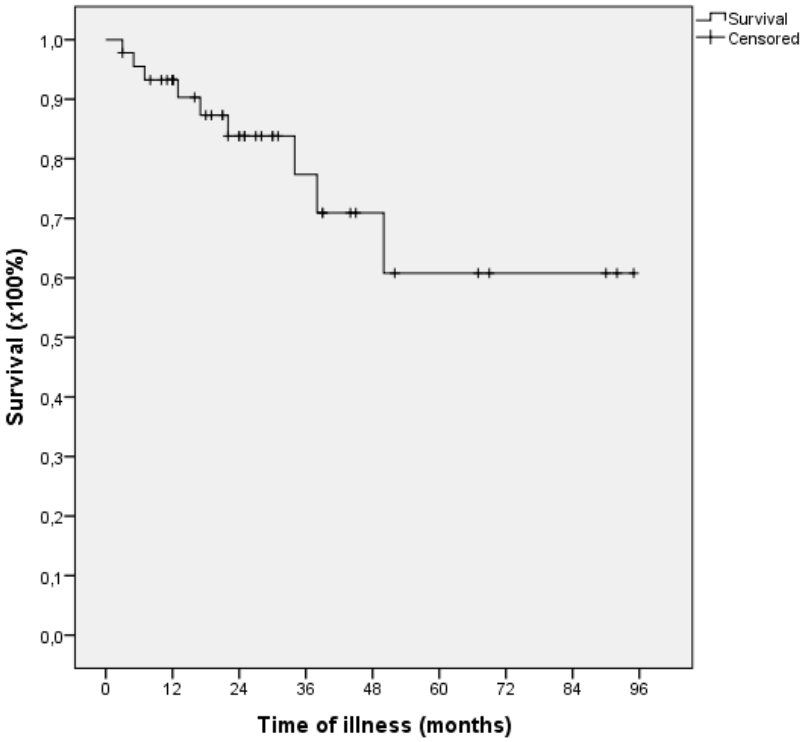

Figure 2. Survival of children with SRNS

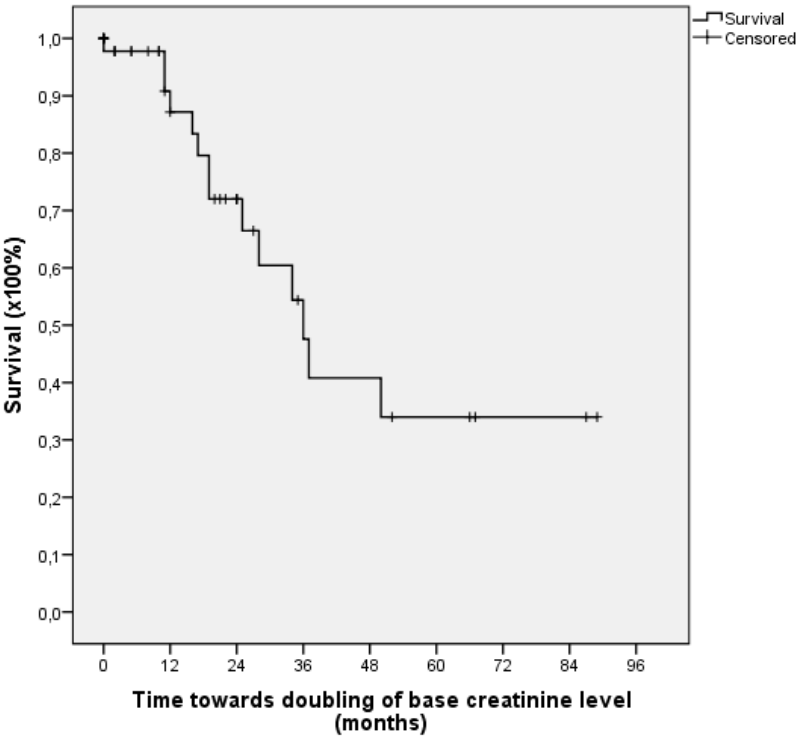

Figure 3. Kidney survival for children with SRNS. Based on lack of doubling of base creatinine levels.

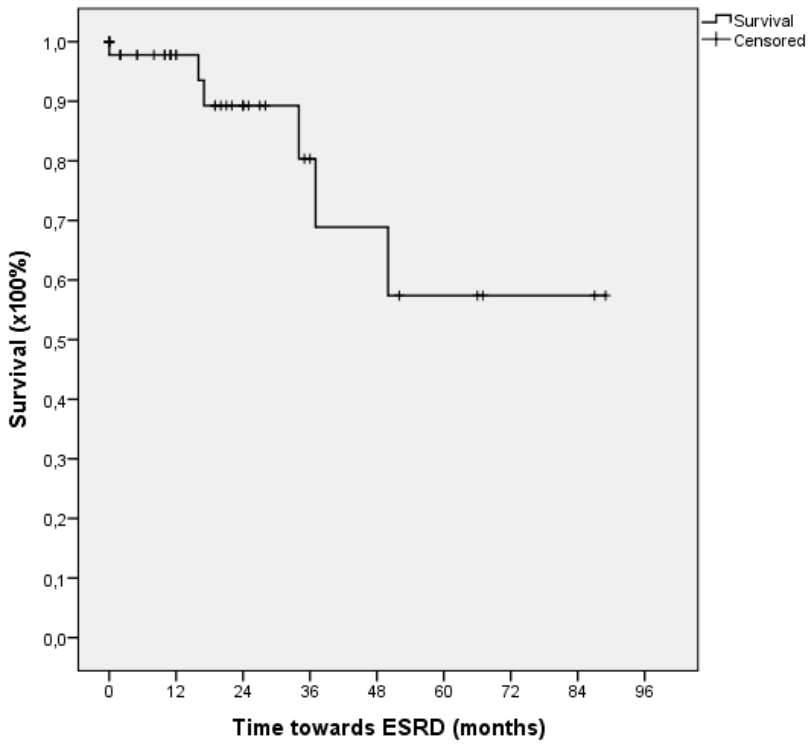

Figure 4. Kidney survival for children with SRNS. Based on lack of ESRD

Kidney Survival Rates

Kidney survival was determined by two measurements: lack of doubling of base creatinine levels and lack of ESRD. The median time of follow up for kidney function was 16 (range 12 to 89) months. We did not have the most recent kidney function data for 19 of 45 patients, 8 of whom were lost to follow up, 3 patients refused to have blood test for kidney function, while in the other 11 patients, the most recent kidney function was obtained from the outpatient clinic data of their last visit. Based on recent kidney function, this study revealed that 5 of 36 patients with CKD stage I at onset, 1 of 6 patients with CKD stage II at onset, while no patients with CKD stage III at onset, developed ESRD.

Kidney survival expressed as a lack of doubling of base creatinine in the fifth year was 34% (range 11.2 to 57.3) (**Figure 3)**, while kidney survival expressed as a lack of ESRD in the fifth year was 58% (range 27 to 88) (**Figure 4).** Fifth year kidney survival rates for each prognostic factor based on lack of doubling of base creatinine levels were calculated. Patients with initial kidney function of CKD stages I, II, III had kidney survival rates of 34%, 0%, and 100%, respectively, with no statistically significant differences (P=0.548). Patients with <10 year age at onset had a kidney survival of 43%, better than that of patients with age of onset ≥10 years at 13%, although not significantly different (P=0.477). Patients with primary resistance had a 44% survival compared to 31% in those with secondary resistance (P=0.276). In addition, the hypertensive group had 0% kidney survival, worse than the non-hypertensive group at 43%, but with no significant difference (P=0.150). Multivariate analysis was not performed since only the hypertension group had a P value of <0.25.

Kidney survival in the fifth year for each prognostic factor based on lack of ESRD were as follows: patients with initial kidney function of CKD stages I, II, III were 63%, 0%, and 100%, respectively, with no significant differences (P=0.721); patients with age at onset <10 years had a kidney survival of 78%, better than that of the ≥10 years group at 19%, although not significantly different (P=0.224); patients with primary resistance had a 52% survival

compared to 75% in those with secondary resistance (P=0.871); and the hypertensive group had a 93% kidney survival, better than non-hypertensive group at 54%, but again with no significant difference (P=0.737). Multivariate analysis was not performed since only the age at onset comparison group had a P value of <0.25.

Discussion

A limitation of this study was the possibility of selection bias due to incomplete access of medical records, since the medical records of inactive patients may have been discarded. Inaccurate and obsolete data in the medical records also posed a challenge, especially for following up patients living outside Jakarta. Also, we did not evaluate the clinical changes during the course of disease, thus the outcomes may have been influenced by other factors not reviewed in this study.

The median of age at onset of our subjects was 5.1 years, similar to those in previous studies.[7,9] There were 82.2% of our subjects with an age at onset of <10 years, with 1.6 times more males than females, also similar to previous studies.[7,9]

We observed a death rate of 20%, much higher than that previously reported.[7] This may be attributed to several factors, such as the differences in treatment given. Patients in this study were initially given cyclophosphamide (CPA), but Mekahli *et al*. and Otukesh *et al*. gave mainly cyclosporine A (CyA) and a combination of CPA with mycophenolate mofetil (MMF).[7,10] A systematic review concludes that CyA was superior for inducing remission compared to placebo or CPA.[11] However, in Indonesia, CyA has not been used for SRNS treatment routinely due to its relatively high price and the technical difficulty in monitoring blood CyA levels. Our treatment was similar to that of a prospective study by Oluwu *et al*. in Nigeria, in which combined CPA-intravenous dexamethasone was followed by oral CPA and prednisone. There was no deaths in their 8-month shorter period of follow up.[9] Sepsis and organ failure as causes of death were similar to those of other study,[7] though the proportion was higher in our study. Kidney survival may also have been affected by infectious causes, since SRNS patients were immunocompromised and prone to infection, although we did not review this factor in our study. In fact, the deaths of SRNS patients were caused by many factors.

Children with CKD stage I at SRNS onset had better survival than the other stage groups, although the differences were not statistically significant. This result may be due to the small number of subjects in each group. Differences in median survival between the CKD stage I, II, and III groups was also not statistically significant (P=0.495), similar to work by Mekahli *et al*. who reported that kidney function at disease onset did not contribute to survival.[7]

Based on age at onset, the decrease in survival rate from the first to fifth years was 17% in the age at onset <10 years group, compared to 69% in age at onset ≥10 years group. However, the lack of a statistically significant difference between these two groups may be due to the small number of subjects. Age at SRNS onset was also not a predictive of response to treatment with immunosuppressive drugs.[10]

Survival of the secondary resistance group was better than that of the primary group, although not statistically significant, which may be due to the difference in proportion and small sample size. Similar results were found by other studies who showed that the primary resistance group had a worse prognosis than that of the secondary resistance group.[9,10] Oluwu *et al*. found that the primary resistance group had mostly histopathologic types of focal segmental glomerulosclerosis (FSGS).[9] We did not examine the histopathology of the children's kidneys to evaluate for FSGS, as kidney biopsy is not performed routinely in our hospital. Some studies reported that children with primary resistance or FSGS have better outcome when be treated with CyA.[7,12]

Survival of children with hypertension at disease onset was not significantly different than those without hypertension, similar to the study by Mekahli *et al*.[7] Larger sample size and longer prospective follow up time may be needed to study the effect of hypertension on survival.

At the end of our study, there were 14 of 45 (31.1%) patients with doubled base creatinine levels, similar to an adult patient study that reported 8% in the therapeutic group and 19% in the non-therapeutic group.[13] Kidney survival in the fourth year, as

measured by the lack of doubling of base creatinine levels, was 56%, higher than that reported by Otukesh *et al*. of 41.8%.[10]

Based on initial kidney function, there was no differences in kidney survival as measured by the doubling of base creatinine levels, possibly be due to the different sample sizes of the groups. Also, 2 out of the 3 patients in the CKD stage III group had routine visits, compared to 3 of 6 patients in CKD stage II, possibly resulting in better kidney survival in CKD stage III. On the other side, based on the age at onset, children with age at onset of <10 years had better kidney survival as measured by the doubling of base creatinine, although the difference was not statistically significantly from the group with age at onset of ≥10 years, possibly be due to the different sample sizes of the groups.

We found that the type of resistance did not contribute to kidney survival based on the lack of doubling of creatinine levels, in contrast to the study by Otukesh *et al*.[10] Furthermore, Mekahli *et al*.[7] found that there was no differences in kidney survival between the hypertensive groups, similar to our findings. However, Fomina *et al*. observed that hypertension was a prognostic factor for reduction of kidney function in children with SRNS.[14]

Six out of 45 (13.3%) patients developed ESRD by the end of our study, fewer than reported by Mekahli *et al*. (29%).[7] Kidney survival based on the lack of ESRD was 58% at the fifth year, also lower than that of Mekahli *et al*. who reported a kidney survival of 75% based on lack of ESRD.[7] However, in the fourth year, our kidney survival rate was higher than that of Oluwu *et al*. (70% vs 41.8%, respectively).[9] These differences may be due to the treatment regimen given. As previously stated, the primary resistance group should be treated with CyA, as we found that the proportion of children with primary resistance developing ESRD was higher than that of the secondary resistance group (25% vs 9%, respectively) using a CPA treatment regimen.

In our study, kidney survival based on lack of ESRD was not influenced by the initial kidney function, similar to results from Mekahli *et al*.[7] Differences in sample size between groups and patient compliance may have affected this result. We also found that children with an age at onset of <10 years had better prognoses for kidney survival based on lack of ESRD. Although this result was not significantly different from the other group, it was consistent with the results of Mekahli *et al*.[7]

A previous study by Otukesh *et al*. concluded that the type of resistance influenced the response to immunosuppressant therapy. They found that the secondary resistance group had better prognoses, 83% at 15 years compared to 34% in the primary resistance group.[10] We found that the secondary resistance group also had better kidney survival based on lack of ESRD, 75% vs 52% in the primary resistance group, although this difference was not statistically significant.

We found no significant differences in the hypertension at disease onset groups, similar to the results of Mekahli *et al*.[7] Median kidney survival of the hypertensive group was 36 months, while that of the non-hypertensive group was 60 months. This result may be due to the differences in time of follow up and sample size proportion between groups. Also, we addressed only hypertension at disease onset, while hypertension during the course of disease may have further contributed to the development of ESRD.

Another prognostic factor for survival of children with SRNS that was not included in our study was histopathology. A previous study found that the type of histopathology noted from kidney biopsy was associated with the outcome of SRNS.[15] In Indonesia, kidney biopsy is not routinely performed in the management of SRNS.

In conclusion, children with SRNS are prone to develop a doubling of base creatinine levels and ESRD. Overall survival of children with SRNS in our study is low. Prognostic factors such as initial kidney function, age at onset, type of resistance, and hypertension at disease onset do not contribute to both patient survival and kidney survival of children with SRNS.

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