Introduction
Mesangiocapillary glomerulonephritis (MCGN), also known as membranoproliferative glomerulonephritis (MPGN), comprises a group of morphologically related but pathogenetically distinct disorders. It is characterized on histology by glomerular hypercellularity, increased mesangial matrix and thickening of peripheral capillary walls with typical deposition of C3 and/or IgG. Characteristically, there is no other immunoglobulin deposition seen on immunofluorescence (IF). The disease is characterized by functional impairment of glomerular basement membrane (GBM) causing progressive loss of renal function that eventually results in end-stage renal disease (ESRD). In 1995, NAPRTCS reported MCGN in 2.8% ESRD cases on dialysis and 3.3% ESRD cases who underwent paediatric renal transplant. The incidence of MCGN varies in different parts of the world and a decline has been reported from most of developed countries. It is estimated that MCGN accounts for 7-10% of total biopsies of acute glomerulonephritis. On the other hand, data on MCGN from developing countries is limited; however, in most reported series, the prevalence is quite high. Reports from Turkey and Nigeria showed MCGN as most frequent histopathologic pattern in nephrotic children who underwent renal biopsy. In contrast to these reports, studies from our hospital found quite low frequency of MCGN as compared to other developing countries. The disease was observed in 3.14% cases in paediatric renal biopsies in a study including nephrotic children and 4.8% in another study including steroid resistant nephrotic syndrome (SRNS) cases. It primarily affects children and young adults with no sex predilection. Clinical presentation and course are extremely variable from benign and slowly progressive to rapidly progressive. Different patterns of presentation include asymptomatic haematuria and proteinuria, acute nephritic syndrome, nephrotic syndrome (NS), chronic kidney disease (CKD) and rapidly progressive glomerulonephritis (RPGN).

There is paucity of data regarding the burden, clinical presentation and outcome of MCGN in children from the developing world. To date, no study is conducted exclusively on MCGN in paediatric population in our...
country. Therefore, the current study was designed to study the frequency, clinical presentation and short term outcome of paediatric patients presenting with MCGN at our hospital.

Methods
It was a descriptive, retrospective, observational study, carried out at the paediatric nephrology department of Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan. Five year record from January 2011 to December 2015 was studied retrospectively. All of these children were treated and followed up as per standard guidelines. The clinical course of the disease and follow-up information related to outcome was retrieved from case notes and patient files. Ethical clearance was obtained from Ethical Review Committee of SIUT.

All paediatric (< 18 years) renal biopsies performed from January 2011 to December 2015 were reviewed retrospectively and cases with histopathological diagnosis of MCGN were selected. Diagnosis of MCGN was based on typical light microscopy (LM) and IF findings. For each patient, data items, including demographics, clinical, and laboratory parameters were noted and entered in a pre-designed proforma which was designed by the principal investigator to enter the relevant data items for subsequent statistical analysis. Spectrum of clinical presentation (RPGN, NS without renal failure (RF), NS with RF) and laboratory investigations including renal functions, urinalysis, renal ultrasound and serology (serum complements, viral markers, antinuclear antibodies, Anti Double Stranded Antibodies, and Anti Streptococcal Antibodies) were noted. Repeat C3 levels, checked after 8 weeks of those patients who had low C3 at presentation, were also recorded. Estimated creatinine clearance was determined by calculating estimated glomerular filtration rate (eGFR) using Schwartz equation. Management included angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) for those who had MCGN without crescents on biopsy and MCGN with crescents was treated according to standard guidelines for crescentic GN. For outcome, each patient was followed till last follow-up or minimum 6 months post diagnosis and categorized as CR, PR, CKD, ESRD, death and lost to follow-up.

Definitions
NS was defined as presence of oedema, proteinuria (urine protein: creatinine ratio >200mg/mmol), or 3+ protein on urine dipstick and hypoalbuminaemia (<2.5g/dl).
Steroid resistant nephrotic syndrome (SRNS) was defined as failure to achieve complete remission after 8 weeks of corticosteroid therapy.

RPGN was defined by rapid loss of renal function (>50% decrease in GFR), acute nephritic illness and normal kidneys on ultrasound.

Recovered/ CR was defined as urine protein: creatinine ratio (<20mg/mmol) or <1 + protein on urine dipstick, serum creatinine normal and no haematuria.

PR was defined as proteinuria reduction of 50% or greater from the presenting value and urine protein: creatinine ratio between 20-200 mg/mmol and serum creatinine normal and/or persistent microscopic haematuria.

CKD was defined as serum creatinine not returning to normal at the end of 3 month follow up period with patient falling in CKD stage 1-4 and not requiring dialysis.

End-stage renal disease (ESRD) was defined as serum creatinine not returning to normal at the end of 3 month follow up period and patient falling in CKD stage 5 requiring dialysis.

Data were entered and analyzed using Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM corporation, Armonk, NY). Only descriptive statistics were carried out. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as frequency (percentage) of cases.

Results
During the 5-year study period, a total of 890 paediatric renal biopsies were performed at our Institute. Among these 63 (7%) children were diagnosed with MCGN. Baseline characteristics of these 63 cases are shown in Table-1. There were 34 (54%) males and 29 (46%) females. Mean age at presentation was 9.9±3.2 years. Majority of patients, 42 (66.6%), had impaired renal functions at presentation and 55 (87.3%) had microscopic haematuria.

Different clinical presentations of MCGN in the chart are shown in Figure-1.

Serum complements in 15 (23.8%) children were normal at presentation and low in 48 (76.2%). Out of the latter, 28
(58.3%) had persistently low complements after 8 weeks of presentation, 15 (31.3%) normal complements at 8 weeks, while 5 (10.4%) children expired before 8 weeks of presentation.

The final outcome according to clinical presentation is shown in (Table-2). It is apparent from the table that highest mortality and rate of ESRD development was seen in those presenting with NS along with impaired renal functions. Relatively better outcome was observed in RPGN group as significant percentage (44.8%) of patients recovered from RF. Follow up of those presenting with NS and normal renal functions at presentation showed that majority of them (47.6%) had persistent proteinuria and microscopic haematuria and sustained normal renal functions, while 7 (33.3%) children, later on, developed renal failure (CKD/ESRD).

MCGN associated with crescents, 28(44.4%), cases was most frequent morphology on biopsy (Figures II) and MCGN with chronic sclerosing GN, was least common, seen in only

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1(1.6%) patient. Patients with cellular crescents, who were treated with intravenous Cyclophosphamide and Methyl Prednisolone with follow up treatment with Azathioprine and Prednisolone, had a good response to treatment, if they clinically had RPGN presentation (Table-3).

Outcome analysis on the basis of morphology (Table-3) showed that highest mortality and rate of ESRD development was seen in those who had MCGN with crescents on biopsy, and favourable outcome was observed in focal segmental MCGN variant with no mortality and lowest percentage of CKD and ESRD development.

In all, 7(11.1%) children died in this cohort. Cause of death included septicaemia in 4(57.1%) patients, dialysis related complications in 2 (28.5%) and one (14.2%) patient died due to massive intracranial haemorrhage. Mean duration of follow-up was 1.66 ± 1.34 years.

**Discussion**

Studies on MCGN show wide variation in its frequency throughout the world. Significantly higher burden has been reported from developing countries like Turkey and Nigeria, where MCGN frequency in childhood NS was found as high as 34% and 51.2%, respectively. On the contrary, very low incidence has been reported from Australia, France, Ireland, Spanish glomerulonephritis registry, making MCGN an uncommon disease in developed world. In our study, frequency of MCGN in paediatric biopsies over 5 years duration was found to be 7% which is almost equal to that observed in another local study done 7 years back, but quite lower than the frequency found in other local studies before the last decade.

Various studies from all over the world show extremely variable clinical presentation of MCGN. We categorized our study patients into two major clinical variants and found NS as the most frequent variant, majority of them had normal renal functions at presentation. Second main clinical variant observed in our study was RPGN. A study from Turkey on paediatric MCGN showed similar findings, as majority 69.7% of their cases presented with NS, 45.5% without RF and 24.2% with RF. Other studies including both children and adult patients with MCGN also reported NS as the most common presenting clinical feature. A retrospective study from Mexico analyzing 30 years data on paediatric MCGN found RF as the most frequent presenting feature, NS in 23.4 % and nephrotic-nephritic syndrome in 25.5%. Asymptomatic presentation of MCGN was not observed in our study as it is mostly encountered on screening and our study is retrospective analysis of patients from a tertiary care hospital managing mostly complicated illnesses and referral cases.

Hypocomplementaemia, a characteristic feature of MCGN, has been reported with variable frequency in different studies ranging from 34.2% in a study from Ireland to 95% from Japan. We observed hypocomplementaemia in 76.2% children at presentation and persistent hypocomplementaemia after 8 weeks of presentation in 58.3% children. The exact reason for these variable findings is not clear. Perhaps, cases with low complement levels represent a different clinical entity.
altogether. Further studies on this rare disorder are required to define this entity further.

As mentioned previously, we diagnosed MCGN on the basis of LM findings and positive IF. Electron microscopy (EM) was not performed on these cases. We observed four morphologic patterns of MCGN in our study, which included MCGN with crescents, which was highest in frequency, followed by diffuse MCGN, focal segmental MCGN and MCGN with chronic sclerosing GN, the latter being the least frequent variant. Similar high percentage of crescentic variant was reported in a study from Turkey on paediatric MCGN.\(^{19}\) On the contrary, very low frequency of crescentic form of MCGN has been reported from most other studies.\(^{23-27}\) In a review by D’Amico et al describing morphologic patterns of MCGN, crescentic form was the rarest finding.\(^{28}\)

We analyzed outcome of our patients on the basis of histological variants and clinical presentation separately. Worst outcome with highest mortality and high rate of ESRD development was observed in crescentic form having sclerosed glomeruli and/or fibrous crescents. This finding is in similarity with other reports showing poor outcome in the presence of sclerosis or crescents on renal biopsy.\(^{29,30}\) We found most favourable outcome in focal segmental MCGN morphology. Alan et al from Ontario also reported focal segmental MCGN as predictor of good outcome.\(^{31}\) Analyzing outcome on the basis of clinical presentation revealed worst outcome in those presenting with NS with impaired renal functions, while NS with normal renal functions had favorable outcome. Patients presenting with clinical RPGN variant (non crescentic GN on biopsy) were observed to have better outcome with low mortality and less frequency of CKD and ESRD development as compared to those presenting with NS and RF. Yilmaz et al\(^{20}\) and Wu et al\(^{22}\) also reported poor outcome in patients presenting with NS along with RF. A study by Schmitt et al describing overall outcome of MCGN in both children and adults reported ESRD in 25.9%, CKD in 26.6% and mortality in 22.7% cases.\(^{32}\)

Our study has certain limitations and weaknesses too. These include retrospective nature of the study, lack of EM study and single center origin of the data. Outcome is documented on the basis of short-term follow-up as MCGN is a slowly progressive disease and long-term follow-up is needed to document the ultimate outcome. Nevertheless, to the best of our knowledge, this is the first study to report the frequency, clinicopathological features, and outcome of paediatric MCGN from our region. We believe that this study will provide base line data for future research on this important paediatric renal disease.

**Conclusion**

Our study reports a low but significant frequency of MCGN in paediatric biopsies from a developing country with majority clinically presenting as NS. Worst short-term outcome with high mortality and ESRD development was observed in those presenting with NS along with impaired renal functions at diagnosis. Patients with focal segmental MCGN had favourable outcome regardless of their clinical presentation. Further prospective studies with long-term follow-up are needed for better understanding, evaluation and management of this disease.

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**References**