

Predictive value of thrombolysis in myocardial infarction risk score analysis for in-hospital and long term survival of patients with right ventricular infarction

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Inferior myocardial infarction (MI) complicated by right ventricular infarction (RVI) is associated with a greater risk of in-hospital mortality¹⁻³ and cardiovascular related complications including heart failure and shock, A-V conduction disorders and tachyarrhythmias, and mechanical complications.¹⁻³ Postmortem studies revealed that there is right ventricular involvement in 19-51% of patients with acute inferior myocardial infarctions.³ In one clinical study its presence was estimated to be approximately 17% in patients with acute inferior or lateral MI.¹ While previous work has established the prognostic role of RVI in patients with inferior MI,¹⁻³ only limited studies to date have attempted to stratify risk among patients with RVI. The development of the Thrombolysis in Myocardial Infarction (TIMI) risk score has provided a useful tool to quickly and easily stratify patients with acute MI. The utility of the TIMI risk score has also been validated in a large acute MI registry.⁴ The purpose of the current investigation was to determine if the TIMI risk score could provide a useful way to risk stratify patients with RVI with regard to short and long-term mortality.

This retrospective study was performed in Tabriz Shahid Madani Heart Center, Tabriz, Iran. Acute MI was diagnosed according to World Health Organization criteria. Five hundred patients who were admitted with the diagnosis of acute inferior wall MI, as first MI, from May 1998 to December 2002 were enrolled in this study. We utilized the following criteria to diagnose RVI in our dataset: the presence of a clinical suspicion of RVI and any of the following, which were present within 24 hours of presentation: 1. ST elevation ≥ 1 mm in V3R or V4R on right-sided precordial chest leads; 2. evidence of right ventricular infarction or dilatation with hypokinesis on echocardiography. The TIMI scores were calculated according to the published criteria.¹ Demographic, clinical, paraclinical data and in-hospital complications were recorded for analysis. According to the above-mentioned criteria, 120 patients with RVI and 380 cases without RVI were detected. Excluding patients

who died during in-hospital period and considering some logistic problems for long term follow up, data for out of hospital study were available for 78 patients in RVI group, which was compared with 154 randomly selected patients in non RVI group. Post hospital survival was evaluated by telephone or periodic visit of patients. Analysis of data was carried out with the Statistical Package for Social Sciences version 11.5 software package. Data was expressed as mean value \pm SD and p -value ≤ 0.05 was considered significant. Of the 500 consecutive patients with inferior wall myocardial infarction, 120 were found to have RVI. The diagnosis of RVI was made by ECG in 91% and echocardiographic criteria in 9%. No significant difference was observed between groups for age, gender, diabetes mellitus, smoking or familial history of coronary artery disease. There was no significant difference in the prevalence of severe systolic LV dysfunction defined as $EF \leq 35\%$ between the 2 groups (RVI: 7.5% versus non-RVI: 7.1%, $p > 0.3$). Patients with RVI were less likely to be treated with beta-blocking agents ($p = 0.001$) and nitrates ($p < 0.001$); no difference was seen in the use of heparin or angiotensin converting enzyme (ACE) inhibitors ($p = 0.9$) or aspirin ($p = 0.2$). Of patients with RVI, 43.2% underwent thrombolytic therapy with streptokinase compared with 31.8% of the patients without RVI ($p = 0.03$). Angioplasty was performed in 6 patients in RVI group compared with 14 cases in non RVI group ($p > 0.05$). In-hospital mortality was higher in patients with RVI than in patients without RVI (RVI: 28.3% versus non-RVI: 8.9%; $p = 0.001$). Similarly, in-hospital AMI related complications were significantly increased in patients with RVI compared to patients without RVI (RVI: 56.7% versus non-RVI: 34.4%; $p = 0.0001$). Specifically, complications due to ventricular arrhythmias (RVI: 10% versus non-RVI: 5.8%; $p = 0.05$), complete heart block (RVI: 34.2% versus non-RVI: 9.1%; $p < 0.001$), mechanical complications (RVI: 3.4% versus non-RVI: 1.4%; $p = 0.5$) and hemodynamic compromise (RVI: 11.7% versus non-RVI: 6.5; $p = 0.028$) were increased in patients with RVI. Considering a mean follow up period of approximately 31 ± 8.7 months out of hospital mortality was more common in RVI group (24.3% versus 12.1% in non RVI; $p = 0.02$) and was more common in females (53% versus males 29%; $p = 0.02$). Application of TIMI scores revealed a strong association between outcome and degree of TIMI score elevation (Figure 1). Of 120 patients with RVI 45 (37.5%) had TIMI score < 4 and 75 (62.5%) had

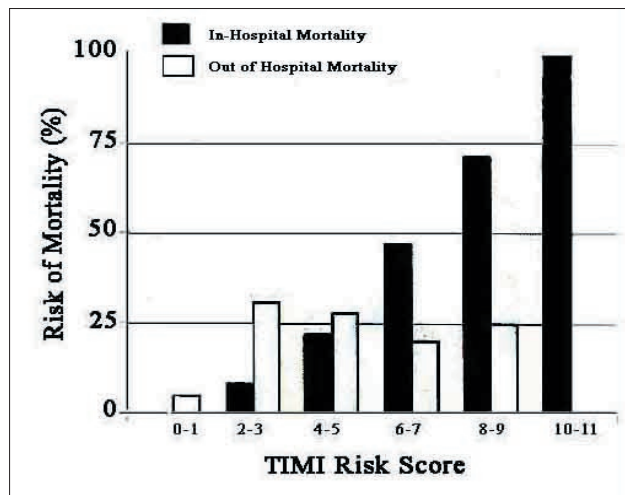


Figure 1 - In-hospital and long term mortality by Thrombolysis in Myocardial Infarction (TIMI) risk score in patients with right ventricular infarction.

TIMI score ≥ 4 . In-hospital mortality was 4.4% in first compared with 42.7% in second group ($p=0.001$, OR=15). Also in-hospital complications were found in 45.5% of first group and 63.2% of second group of patients ($p=0.05$). There was no significant difference in out of hospital mortality between the 2 groups (TIMI score < 4 : 18.6% versus TIMI score ≥ 4 : 25.5%; $p=0.35$). We observed a significant association between each one point increase in the TIMI score and in-hospital mortality (OR=3.56, $p<0.001$) but such a correlation could not be found between TIMI score and long-term survival ($p=0.15$). Clinical data provide clear evidence that patients with inferior MI who have right ventricular (RV) myocardial involvement are at substantially increased risk of major complications, including death, cardiogenic shock and ventricular arrhythmias.¹⁻³ In our study in-hospital mortality was 3 times more common in RVI group, similar to findings of Gumina et al¹ and Mehta et al.² Meanwhile, the lack of any difference in the prevalence of significant left ventricular (LV) dysfunction between these 2 groups, as demonstrated in our study (RVI: 7.5% versus non-RVI: 7.1% $p>0.3$), indicates that the adverse prognosis in patients with RV myocardial involvement is not simply due to more extensive infarction of the LV; rather, it appears to be due directly to involvement of the RV.² In our study, similar to others,^{1,2} in-hospital complications were significantly more common in RVI group. The worse prognosis in patients with RV myocardial involvement may be related to these increased complications, as increased risk of life-threatening ventricular arrhythmias, atrioventricular block, sustained VT and

VF. To our knowledge, only one study has established a prognostic measure within RVI patients alone.¹ The development of the TIMI risk score has created a useful tool with which to risk-stratify patients with acute MI. It has been validated in a large, non-selected registry of AMI patients.⁴ Our observations extend previous work by demonstrating the utility of the TIMI risk score to patients with RVI. With increasing TIMI risk score in hospital mortality increased stepwise from 0 in TIMI risk score 0-1 to 70.5% in those with TIMI risk score ≥ 6 . However, unlike our study, there was no further increase in mortality with risk scores beyond 4-5 in the Gumina et al¹ study. In this study the number of patients within each score group was not reported, so we could not find a definite description for this results. One possible cause may be related to higher rate of reperfusion therapy in the Gumina et al¹ study (61.8%) compared with our study (48.2%), which led to decreased mortality of high score patients. In our study, every one point increase in TIMI risk score was associated with $3.5 \pm 1.4\%$ ($p<0.001$) increase in in-hospital mortality. In our study out of hospital mortality in a mean follow up period of approximately 31 ± 8.7 months was 24.3% in RVI and 12.1% in non RVI group ($p=0.02$). The long-term prognosis of patients with right ventricular infarction has not been well defined. Berger et al³ identified 58 patients with right ventricular dysfunction out of 1110 patients undergoing predischarge radionuclide ventriculography in the TIMI-2 trial. Right ventricular function had returned to normal by 6 weeks in over 80% of patients, and the initial right ventricular dysfunction was not associated with increased mortality at 1 year.³ In addition, using echocardiography, Keitkoglu et al⁵ showed significant improvement in RV systolic and diastolic function 3 months after acute RVI. However, other studies have shown that right ventricular dysfunction may persist,³ and if it does, it predicts an adverse long-term outcome. The differences in these studies may depend upon whether the patients studied had true right ventricular infarction or ischemia with resultant right ventricular stunning that subsequently recovered completely. The prognosis may also be different if patients receive reperfusion therapies. Prompt and complete reperfusion of the right ventricle dramatically improves right ventricular function and hence, the clinical outcome.⁶ So increased mortality of RVI patients in our study may be related to lower rate of reperfusion therapy (specially angioplasty) in our patients and higher rate of persistent RV dysfunction. For example, the rate of primary angioplasty in RVI group was 61.8% in Gumina et al¹

study versus 5% in our patients. In our study there was no significant correlation between TIMI risk score and long term mortality (TIMI score <4: 18.6% versus TIMI score \geq 4: 25.5%; $p=0.35$). Considering the fact that only 78 patients underwent long term follow up, we suppose that this finding should be evaluated at a larger series, but in present study, the explanation for this finding is related to the nature of parameters in TIMI risk score since parameters like systolic blood pressure, heart rate and Killip class may indicate to acute ischemia and acute left or right ventricular ischemia that resolves with routine treatments with no long term effect. Therefore, there is no place for increase in long term mortality with increase in TIMI risk score.

The RVI leads to significant increase in in-hospital mortality and morbidity of acute inferior wall infarction that can be predicted accurately with TIMI risk score system. Lack of early reperfusion therapy may lead to increased long term mortality of these patients, which could not be predicted accurately using this system.

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An analysis of patients diagnosed with pulmonary embolism in terms of clinical and meteorological data

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Pulmonary thromboembolism (PTE) is a major cause of morbidity and mortality. In this study, it is aimed to analyze the patients diagnosed with PTE through cluster analysis, a multivariate classification method, in order to establish whether there were classifications in terms of epidemiological, clinical, seasonal and meteorological variables.

Patients files of 49 patients diagnosed with PTE in our clinic between 1999 and 2003 were inspected retrospectively. Patients whose diagnose were confirmed with lung perfusion scintigraphy and contrast-enhanced spiral computed tomography were enrolled in the study. As the impact of meteorological factors was to be investigated, those coming from cities other than Bursa were excluded. All patients enrolled were evaluated for protein-C, protein-S, and antithrombin III values. They were also examined with Doppler ultrasonography with respect to deep vein thrombosis (DVT). Patients were also assessed in terms of PTE predisposition factors. Obesity (body mass index >28 kg/m²), major abdominal-pelvic surgery, knee-hip surgery, postoperative intensive care, pregnancy, postpartum period, use of oral contraceptives, acute myocardial infarct, congestive heart failure, malign diseases, history of trauma, and immobility were regarded to be predisposition factors. Patients with PTE were analyzed with respect to the months and seasons. In order to investigate the association between PTE and meteorological factors, data regarding temperature, humidity and air pressure were obtained from State Meteorological Services in Bursa for the days, which embolism events were observed.

In this study, the data were analyzed using the cluster analysis method. The data set included mixed type measures. Therefore, Gower similarity coefficient was used to compute the similarity between individuals. Single linkage method was used for merging clusters. After description of the clusters, for determining the variables, which make the difference in the formation of the clusters, Mann-Whitney U test and Fisher's exact test were used. Statistical significance was set as

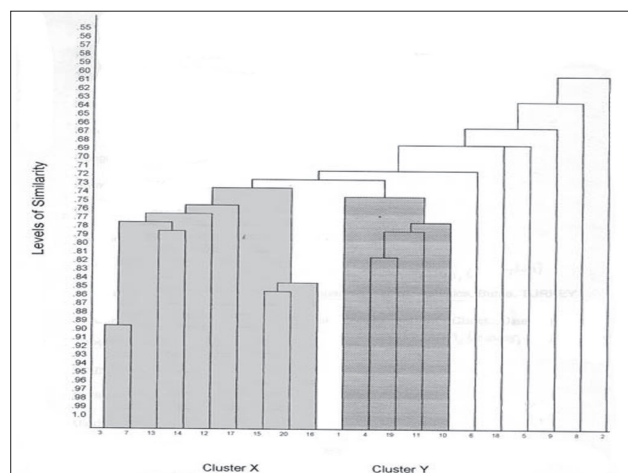


Figure 1 - Dendrogram indicating classification of patients regarding levels of similarity.

$\alpha=0.05$. In order to statistically evaluate the patients through clustering method, 20 patients possessing all pre-disposition factors of pulmonary embolism were enrolled in the study. Of these, 14 (70%) were males, 6 (30%) were females, with a mean age of 49.30 ± 3.53 (mean \pm SEM) years. A total of 2 clusters were established at a similarity level of 0.723. Of the 20 patients, 14 (70%) were formed into clusters. The remaining 6 (30%) patients were regarded to be controversial units. The dendrogram indicating the classification of the patients in terms of their levels of similarity is given in **Figure 1**. No significant differences were established between the clusters in terms of protein-C, protein-S and antithrombin III values ($p>0.05$). One patient in each cluster was observed with DVT and therefore, no significant difference was established between the clusters in terms of DVT ($p>0.05$). Of the patients in cluster X, 3 patients were established with predisposition factors. However, no statistically significant differences were observed between the clusters with respect to predisposition factors ($p>0.05$). All the patients in this present study were assessed regarding the factors known to lead to pulmonary embolism. Statistical analysis revealed that patients were similar and were formed into 2 groups. While age, protein-C, protein-S, antithrombin III, gender, predisposition factors (prolonged bed rest, obesity, long journey, anamnesis, and so forth) and DVT were observed to have no impact on the formation of cluster X, consisting of 9 patients, and cluster Y, consisting of 5 patients; season, month, temperature, and air pressure were noted to have been effective. While the mean temperature was $21.46 \pm 1.85^\circ\text{C}$ in cluster X at the time of embolism

diagnosis, it was $4.38 \pm 0.85^\circ\text{C}$ in cluster Y ($p<0.01$). The mean value for air pressure was 999.84 ± 0.98 Mb for cluster X, ($p<0.05$), and 1007.04 ± 2.29 Mb for cluster Y, ($p<0.05$). Distribution of the patients with respect to months demonstrated a significant difference for the month of January ($p<0.001$). All of the embolism cases in cluster X had occurred in the months other than January. Similarly, 4 (80%) out of the 5 patients in cluster Y had been diagnosed with embolism in January. When embolism cases were analyzed regarding the seasons, it was noted that all the patients in cluster X had experienced embolism in seasons other than winter; all the patients in cluster Y had experienced embolism in winter ($p<0.001$).

Our study established that seasonal variations in temperature and air pressure had an impact on pulmonary embolism incidence. It was observed that patients with pulmonary embolism had been grouped into 2 clusters, which had no differences in terms of age, gender, severity and predisposition factors. The determinant factors in the clusters were demonstrated to be the differences in temperature and air pressure. Seasonal variations in venous thromboembolic diseases have often been associated with meteorological variables such as temperature, humidity and air pressure. The increase observed in venous thromboembolism is attributed to hypercoagulation induced by cold weather; peripheral vasoconstriction and limited mobility in winter months. The incidences of aortic dissection, sudden cardiac death, stroke, and venous thromboembolic diseases have been reported to be subject to seasonal variations.^{1,2} The increase in venous thromboembolic diseases in winter months has been stated in various studies. A study conducted in France, evaluating nationwide hospital records between 1995 and 1998, assessed 65,081 DVT and 62,237 PTE cases. The study revealed a significant increase in DVT and PTE incidences in winter.³ Similarly, Sharma et al⁴ reported 2.9 times higher incidence of non-fatal PTE in autumn and winter than summer and spring in their study evaluating 248 non-fatal PTE patients. In this present study, it was observed that all of the patients in cluster Y had experienced embolism in winter. The most extensive study on seasonal variations in venous thromboembolism was carried out on 2,457,000 PTE and 5,767,000 DVT cases between 1979 and 1999 in the USA. The study which reviewed all hospital records nationwide reported that there were no significant differences in terms of seasons or months.⁵

Clauss et al⁶ investigated the influence of environmental factors such as temperature, vapor pressure, air pressure, rainfall, and humidity on

pulmonary embolism incidence. They reported that pulmonary embolism incidence was correlated positively with vapor pressure and rainfall. Our study did not take rainfall, but air pressure was observed to be a factor with an impact on pulmonary embolism incidence, consistent with the above mentioned study. Various proposals have been made to explain the association between venous thromboembolism and seasonal factors. Patients in this study were observed to have formed 2 similar clusters. Temperature and air pressure were the differences between the clusters. We established that predisposition factors to pulmonary embolism did not differ between the clusters. The number of patients in our study was limited since we enrolled only the patients who possessed all predisposition factors.

In conclusion, this present study which is aimed to analyze the patients with pulmonary embolism through cluster analysis, a multivariate classification method, revealed that clinical variables did not have an impact on the formation of the clusters and seasonal factors were associated with the classification of patients with pulmonary embolism, and that these factors may have an impact on clinical variables.

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Busulfan induced myoclonus

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Busulfan is an alkylating chemotherapeutic agent. In combination with other chemotherapeutic drugs, it is an acceptable preparative (conditioning) agent before bone marrow and peripheral blood stem cell transplantation. Busulfan rapidly enters the central nervous system (CNS) and may cause seizures when used in a high dose.¹ Consequently, patient should receive prophylactic phenytoin (with therapeutic level) to begin before busulfan and continued for 24 hours after the last dose. There is a wide intra- and interindividual variation of absorption and metabolism of busulfan. In addition, pharmacokinetic differences exist between age groups.

Our patient is a 16-year-old Omani lady with precursor B cell acute lympholytic leukemia, diagnosed on September 2004. She has an unremarkable medical history. She was started on chemotherapy. As cytogenetic study showed Philadelphia chromosome positive, that put her at a high risk of relapse, it was decided to proceed to allogeneic bone marrow transplantation as early as possible in the first remission. She was admitted to bone marrow transplantation unit on April 2005, her body weight was 39 kg, height 154.6 cm and body surface area 1.3 m.² The preparative regimen consisted of fludarabine and busulfan.³ Aiming at decreasing the regimen related to toxicity, a busulfan pharmacokinetic study was performed.² Two days before starting the regimen, a study was carried out using a busulfan test dose as a guide to the appropriate actual dose. This was followed by monitoring of the serum busulfan level throughout the regimen.⁴ Phenytoin was started before the Busulfan (BU) test dose, continued through the regimen and until 24 hours after the last dose of BU. She received an oral stat dose of phenytoin 300 mg, followed by 100 mg tid oral. Serum free phenytoin level before starting BU was 3.5 umol/l (therapeutic range 3.3-9.6). The 4th day regimen consisted of a single daily intravenous (iv) dose of BU and fludarabine. On the first and second days she received daily 140 mg BU, while on the third and fourth she received daily 160 mg, guided by the prior regimen study and serum level monitoring. After receiving the last dose of BU, she developed for a few second a generalized myoclonus. Again and after the fourth hour of this episode, she

had an interrupted repeated myoclonus, each last for few seconds. This cluster of seizures spontaneously stopped and did not recur. She never had lost her consciousness. Clinical examination did not show any neurological abnormality. Since admission till the onset of the convulsions she had normal temperature, O_2 saturation, serum electrolytes and serum glucose. As planned she received peripheral blood stem cells transplantation on twelfth and thirteenth February 2005, and she was successfully engrafted on 1st March 2005.

Phenytoin is a widely used prophylaxis to prevent BU induced seizures. The researches in this field virtually studied the conventional daily 4 doses of oral BU, while in this study we used the single daily dose of iv BU regimen.³ Our patient had seizures in spite of a prior regimen pharmacokinetic study, monitoring of serum BU level and achieving a therapeutic serum phenytoin level. More research is expected to study this single daily dose iv BU regimen and there may be a need to investigate for other(s) effective and safe alternative seizures prophylaxis.⁵

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Chlorambucil therapy in children with steroid-resistant nephrotic syndrome

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Chlorambucil (CHL) had been used as treatment for childhood nephrotic syndrome (NS) for more than half a century.¹ It was used mainly in children with steroid sensitive nephrotic syndrome (SSNS) as steroid sparing agent in those with frequent relapsing or steroid dependent course.² However, it was observed to result in higher rates of severe side effects and recommended as a second line drug after cyclophosphamide (CYC), which is considered as safer alkylating agent.² The alkylating agents have been used for treating steroid resistant nephrotic syndrome (SRNS).² However, CYC was used in most of the studies,³ while CHL was used only rarely.^{4,5} Elzouki et al showed in a small study that CHL induced complete or partial remission in patients with SRNS caused by either focal segmental glomerulosclerosis (FSGS) or mesangial proliferative glomerulonephritis (MPGN).⁴

In this retrospective study, we report our results of using CHL in children with SRNS secondary to IgM nephropathy, FSGS or diffuse mesangial hypercellularity (DMH). All patients presented to our unit over 20 months period (from February 2002 until June 2004) and were diagnosed as SRNS were recruited. Steroid resistant nephrotic syndrome was defined as a failure to go into remission after 4 weeks of prednisolone therapy at a dose of 60 mg/m²/day, plus 3 intravenous doses of methylprednisolone (600 mg/m²/day or 30 mg/kg/day) on alternate days. We had 7 patients with SRNS. All patients were females. The median (range) age at presentation was 4 (2-9) years. All except 2 were Arab in origin. All studied children were primary non-responders to prednisolone and 2 were also resistant to intravenous cyclophosphamide course. All the 7 children were treated with CHL (0.1-0.2 mg/kg/day) for 8-12 weeks. The mean \pm SD accumulative dose was 10.1 \pm 3.3 (7.0-15.2) mg/kg. All patients were continued on oral prednisolone 40mg/m² on alternate days and received enalapril (0.5-1 mg/kg) throughout the CHL therapy. Two patients achieved complete remission after 12 weeks of CHL therapy. One patient remained in remission for 2 years following CHL therapy and one patient had a relapse once after 1.5 years of follow up, which responded to prednisolone promptly. She had been on

Table 1 - Laboratory data before and after chlorambucil therapy in individual patients.

Patient's no.	Age at onset (years)	Sex	Histo-pathology	Pre-therapy			Duration of therapy (weeks)	Accumulative dose (mg/kg)	Post-therapy		
				S. alb (g/l)	S.cr (umol/l)	Urine protein			S. alb (g/l)	S.cr (umol/l)	Urine protein
1	4	F	IgM nephropathy	19	21	3+	12	14	37	22	-ve
2	2.5	F	IgM nephropathy	6	20	3+	12	15.2	38	24	-ve
3	2	F	DMH	4	19	3+	8	10.3	6	10	3+
4	5	F	IgM nephropathy	23	13	3+	8	8.6	24	11	2+
5	3.5	F	IgM nephropathy	15	31	3+	8	7.3	19	35	3+
6	7.5	F	IgM nephropathy	10	41	3+	8	8.5	10	68	3+
7	9	F	FSGS	21	85	3+	8	7	29	55	2+

F - female, IgM - immunoglobulin M, DMH - diffuse mesangial hypercellularity, FSGS - focal segmental glomerulosclerosis, S.alb - serum albumin, S.cr - serum creatinine, -ve = negative

one year remission. Two patients received CYC of 500 mg/m² per month for 6 doses before CHL therapy. The rest of the patients did not respond after 8 weeks of CHL therapy (Table 1). All of them except one were treated subsequently with Cy A. Two patients achieved complete remissions on Cy A while one patient achieved partial remission only. One patient was treated with CyA initially as the histopathology showed FSGS. However, she was treated with CHL when she showed sign of CyA toxicity and achieved partial remission after 8 weeks. No side effect was observed in any of the patients. None of the patients had leucopenia, hemorrhagic cystitis, infection, vomiting or alopecia. Our finding suggests that CHL is of therapeutic value in inducing remissions in children with SRNS secondary to IgM nephropathy. This agrees with previous reports of using it in SRNS caused by other histopathological forms.^{4,5} Pascual et al reported that CHL is effective in SRNS caused by MCD5 and Elzouki et al reported that CHL induced complete remission in 3 out of 4 patients with FSGS.⁴ One patient in this study experienced partial remission and one patient with SRNS caused by MPGN achieved complete remission. The 2 children who achieved complete remission in our study received 12 weeks course of CHL and higher accumulative dose (15.2 and 14mg/kg) than the non-responders who received 8 weeks course with a lower accumulative dose. We did not observe any side effects in our patient. However, CHL is known to cause many side effects.² Leucopenia occurs in approximately one of 3 patients receiving CHL and infection in 6.3%.² Children who received CHL are also at increased risk of developing malignancies (approximately 0.6%). However, the reported cases received longer duration and higher total accumulative total dose.^{2,4} The Gonadal toxicity is also a risk with CHL therapy particularly in males.²

It was estimated that CHL at a dose of 17 mg/kg with concomitant steroid may be safe.² However, the risk is minimized with a total dose of 7-10 mg kg. Seizures were also reported in 3.4-8% of children treated with CHL.²

We conclude that CHL therapy in a total accumulative dose of 15 mg/kg and 12 weeks duration could achieve complete remission in children with SRNS secondary to IgM nephropathy. Further randomized controlled studies are required.

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