MYASTHENIC CRISIS – ANALYSIS OF PREDISPOSING FACTORS, CLINICAL FEATURES, COMPLICATIONS AND TREATMENT OUTCOME

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CERTIFICATE

This is to certify that the dissertation entitled **"MYASTHENIC CRISIS – ANALYSIS OF PREDISPOSING FACTORS, CLINICAL FEATURES, COMPLICATIONS AND TREATMENT OUTCOME"** is a bonafide record of work done by **Dr.M.JAYAKUMAR** in the Institute of Neurology, Rajiv Gandhi Government General Hospital & **MADRAS MEDICAL COLLEGE, CHENNAI** in partial fulfillment of the Tamilnadu Dr.MGR Medical University rules and regulations for the award of **D.M. (NEUROLOGY)** degree under my direct guidance and supervision during the academic year **2011-2014**.

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DECLARATION

I solemnly declare that this dissertation titled **"MYASTHENIC CRISIS – ANALYSIS OF PREDISPOSING FACTORS, CLINICAL FEATURES, COMPLICATIONS AND TREATMENT OUTCOME"** is done by me in the Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai under the guidance and supervision of Prof. Dr. K. BHANU, Dip. NB., D.M., Professor of Neurology, Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to the Tamil Nadu Dr.MGR Medical University, Chennai in partial fulfillment of the university requirements for the award of the degree of D.M. Neurology**.**

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CONTENTS

INTRODUCTION

Myasthenia gravis is a neuro-muscular junction disorder characterized by skeletal muscle weakness and fatiguability. It is due to a decrease in the number of available acetylcholine receptors at the neuromuscular junction as a result of antibody mediated autoimmune attack.

Weakness of muscles may involve cranial and somatic musculatures. Weakness resembling myasthenia gravis may occur in other conditions as a result of drug, endocrine disease of thyroid, certain malignancies, bacterial toxins and also by non-autoimmune mechanisms involving the neuromuscular junction.

The weakness may involve all the skeletal muscles of the body but the distribution of weakness has a characteristic pattern and there is a diurnal variation of symptoms. If the weakness of respiratory muscles becomes so severe as to require respiratory assistance, then it is called myasthenic crisis.

The myasthenia may be generalized one involving all the groups of muscles or it may involve the extra ocular muscles and facial muscles. Sometimes the bulbar muscles alone may be involved and the condition is called bulbar myasthenia gravis.

In some of the patients, (anti-AchR) Acetyl choline receptor antibodies may be positive and in some it will be negative. In some of the patients, anti-muscle specific tyrosine kinase antibodies will be positive and negative in some of the patients.

AIM OF THE STUDY

- To study the predisposing factors, clinical features, associated complications and treatment outcome in patients with myasthenic crisis.

REVIEW OF LITERATURE

MYASTHENIA GRAVIS AND CRISIS

Epidemiology:

Myasthenia gravis can occur in any age group from infancy to old age. There is a considerable variation in the incidence and prevalence of myasthenia around the world [12]. Biological and genetic factors play a role for this variability. In the United States, the prevalence rate is 20 per 100000 population with a total of 60000 cases [1].

Gender and age influence the incidence of Myasthenia gravis. The disease is three times more common in women than men before the age of 40 years. The incidence is higher in males after 50 years of age. The incidence is equal during puberty.

Pathophysiology

Acetyl choline is synthesized in the motor nerve terminal at the neuromuscular junction and is stored in vesicles. When an action potential reaches the nerve terminal, Ach is released from 150-200 vesicles and this

combines with Acetyl choline receptors which are densely packed at the peaks of post synaptic folds. The structure of acetyl choline receptor consists of five sub units – 2α, 1β, 1∂ and 1γ or ε arranged around a central pore. When acetyl choline combines with the binding sites on the α subunits of AchR, the channel in the AchR opens, resulting in rapid entry of cations, especially sodium, causing depolarization of the end plate region of muscle fibre. If the depolarization is large enough, it causes an action potential that spreads along the muscle fibre, initiating muscle contraction. This process is rapidly terminated by hydrolysis of Ach by acetylcholinesterases which is present in the synaptic folds and diffusion of Ach away from the receptor.

In Myasthenic gravis, the defect is a decrease in the number of available AchRs at the post synaptic muscle membrane and the post synaptic folds are flattened resulting in decreased efficiency of neuromuscular transmission. Even though Ach is released normally, it produces small end plate potentials that fails to trigger muscle action potentials. Failure of transmission at multiple neuromuscular junctions causes weakness of muscle contraction.

The amount of Ach released for each impulse normally declines on repeated activity (called presynaptic rundown). In myasthenic patients, the decreased efficiency of neuromuscular transmission combined with normal

rundown results in the activation of fewer and fewer muscle fibres by successive nerve impulses and hence increasing muscle weakness. This accounts for decremental response to repetitive nerve stimulation on electrodiagnostic testing.

In myasthenia gravis, the neuromuscular abnormalities are brought about by an autoimmune response mediated by specific anti-AchR antibidoes. The anti-AchR antibodies reduce the number of available AchRs at the neuromuscular junctions by three mechanisms.

i) Accelerated turnover of AchRs by cross-linking and rapid endocytosis of receptors.

ii) Blockade of active site of AchR

iii) Damage to the post synaptic muscle membrane by antibody and complement.

An immune response to muscle-specific kinase (MUSK) can also result in myasthenia gravis by interfering with AchR clustering. The pathogenic antibodies are IgG and are T-cell dependent.

Immunopathology:

The AchR antibodies bind to AchR on the terminal expansions of the junctional folds and cause complements mediated destruction of folds and increased degradation of AchR. These antibodies block Ach from binding to

AchR [29]. Destruction of the junctional folds leads to simplication and distortion of the post-synaptic region and functional loss of AchR. This causes neuromuscular transmission failure and muscle weakness [29]. CD4 T cells are present in increased numbers in these patients which regulate the AchR antibody production. The α-subunit of AchR bears T-cell recognition sites. Sensitization to CD4 T-cells occurs on the AchR complex and the T-cells recognize multiple epitopes on the AchR α-subunit [14]. Low affinity IgG antibodies are reported in two-thirds of myasthenic patients who are seronegative[30]. Many subtypes of myasthenia gravis are identified basing on clinical presentation, age of onset, thymic pathology and autoantibody profile[12].

Generalised MG:

Generalised myasthenic gravis may be either early onset or late onset type. Early onset myasthenia gravis occurs in females before 40 years of age, have anti Ach-R antibodies and enlarged hyperplastic thymus gland. Late onset disease occurs in males, have antibodies to striated muscle proteins like titin, and ryanodine receptors in addition to Ach-R antibodies. The presence of anti-muscle antibodies, especially anti-ryanodine receptor antibodies is associated with more severe generalized or oropharyngeal weakness and myasthenic crisis [33].

Thymomatous MG:

Thymoma is present in 10% to 15% of myasthenia gravis. Thymoma associated myasthenia has equal frequency in males and females and may occur at any age with peak age of onset at 50.

In myasthenia gravis, the thymas is abnormal in 75% of patients. In 65% the thymus is hyperplastic with active germinal centres and the hyperplastic thymus is not necessarily enlarged. 10% of patients have thymomas. Muscle like cells within the thymus which bear AchRs on their surface serve as a source of autoantigen and trigger the autoimmune reaction within the thymus gland. Neoplastic epithelial cells in thymomas express numerous self-like antigens, including AchR, titin and ryanodine receptor-like epitopes. The regulation of auto reactive T-cells may be impaired in thymoma due to a deficiency in the expression of the autoimmune regulator gene and selective loss of T-regulatory cells in human thymoma.[(12)]

Clinical Features:

The clinical manifestation of myasthenia gravis is weakness and fatiguability of muscles. The weakness increases during repeated use and improves after rest or sleep. The course is variable. Exacerbations and remissions may occur during the first few years after the onset of the disease. Remissions are rarely complete or permanent. Any systemic

disorders or unrelated infections often precipitates increasing myasthenic weakness and causes crisis.

The weakness of muscle has a characteristic pattern of distribution. The lids and extra ocular muscles are often affected early in the course of myasthenic gravis and diplopia and ptosis are the initial symptoms. Later facial and oro-pharyngeal muscles are affected. Facial weakness produces a snarling expression when attempting to smile. Weakness in chewing is noticeable after prolonged effort. Difficulty in swallowing may occur due to weakness of palate, tongue or pharynx resulting in nasal regurgitation, aspiration of liquids or food. Speech will be of nasal timbre due to weakness of palate or a dysarthric mushy quality due to tongue weakness. Bulbar weakness is common in Musk antibody positive Myasthenia gravis. In 85% of patients, the weakness is generalized, affecting the limb muscles as well. If weakness is restricted to the extracular muscles for 3 years, it is unlikely that it will become generalized, and they are classified to have ocular myasthenia gravis. Asian patients have predominant ocular myasthenia gravis in upto 58% of all myasthenic patients. The limb weakness in myasthenia gravis is often proximal and asymmetric. Inspite of weakness, deep tendon reflexes are preserved. If the respiratory muscles become weak, it requires respiratory assistance and the patient is said to be in crisis.

Association of Myasthenic Gravis with other diseases:

Myasthenic gravis is associated with other immune mediated diseases like hyperthyroidism, rheumatoid arthiritis, seizure in children, diabetes mellitus and extra thymic neoplasm. Extra thymic malignancies are reported in older age patients and is possibly due to immune dysregulation. [38]

Diagnosis:

The diagnosed is based on the typical distribution of weakness and fatiguability without loss of reflexes or impairment of sensation or other neurologic function. The diagnosis is confirmed by investigatiosn because;

1. Other treatable conditions may resemble myasthenia gravis and
2. The treatment of myasthenia gravis may involve surgery and the prolonged use of drugs with its adverse side effects.

Antibodies to AchR or Musk:

Anti-AchR antibodies are detectable in the serum of 85% of all myasthenic patients but in 50% of patients with ocular myasthenia gravis. The presence of Anti-AchR antibodies is diagnostic of myasthenia gravis and negative test does not rule out the disease. The measured level of antibodies do not correspond with the severity of disease but a treatment induced fall in antibody level correlates with clinical improvement. Anti-musk antibodies are present in 40% AchR antibody negative generalized myasthenia gravis patients. Musk antibodies are rarely present in AchR

antibody positive patients or in patients with MG limited to ocular muscles. There in evidence that Myasthenia gravis patients without antibodies to AchR or Musk have undefined antibodies that impair neuromuscular transmission. Antistriational muscle antibodies occur in increasing frequency in older patients and in patients with more severe disease. This suggests that disease severity is related to humoral response against multiple muscle antigens. [33]

Electrodiagnostic Testing:

Repetitive nerve stimulation:

Anti-AchE medication is withheld 6-24 hours before testing. Weak muscles are tested by delivering electric shocks of 2-3 Hz per second to appropriate nerves and action potentials are recorded from the muscles. In myasthenic patients, there is a rapid reduction of >10-15% in the amptitude of the evoked responses. A single dose of edrophomium is given to prevent or diminish this decremental response as a further test. The sensitivity of RNS is diagnosing Myasthenia Gravis is from 53% to 100% in generalized myasthenia gravis and in ocular myasthenia gravis it is 10% to 48% [35]. The most sensitive test of neuro muscular transmission is the single fibre EMG. There is increased jitter in some muscles in all patients with Myasthenia Gravis [35]. The jitter can be measured with concentric needle electrode as an alternative to specially designed single fibre electrode [36].

Edrophonium Test:

Drugs that inhibit the enzyme AchE allow Ach to interact repeatedly with the limited number of AchRs, producing improvement in the strength of myasthenic muscles. Edrophonium is used for diagnosis because of its rapid onset of action (30 sec) and short duration (5 min) of its effects. The weakness of extra ocular muscles, impairment of speech or the length of time that the patient can maintain the arms in forward abduction are evaluated. Initially, 2mg of edrophonium i.v. is given. If there is definite improvement, the test is positive and is stopped. If there is no change, an additional 8mg iv is given either in two parts or single dose because some patients develop side effects like nausea, diarrhoea, salivation, fasciculation and rarely of syncope or bradycardia. These side effects are reported in 0.16% edrophonium tests. If there is troublesome side effects, atropine iv be given.

False positive tests occur in other neurologic disorders like amyotrophic lateral sclerosis, in placebo reactors, Eaton-Lambert syndrome, intracranial aneurysm, brainstem lesions, congenital myasthenic syndrome, cavernous sinus tumors, end stage renal disease and muscle disease affecting the ocular muscles. False-negative (or) equivocal tests may also occur. The edrophonium test is reserved for patients with clinical findings

suggestive of myasthenia gravis but who have negative antibody and nerve conduction studies. The edrophonium test is positive in 60% to 95% of patients with ocular myasthenia gravis and in 72% to 95% of generalized myasthenic gravis [15]. The optimal edrophonium dose can not be predetermined. The average dose of edrophonium to give a positive response was 3.3mg for ptosis and 2.6mg for dysfunction of ocular muscles [16].

Congenital myasthenic syndromes:

These are a heterogenous group of disorders of neuromuscular junction that are not autoimmune but are due to genetic mutations in which any component of the neuromuscular junction may be affected. Alteration in function of presynaptic nerve terminal or in the various subunits of the AchR or AchE have been identified. The congenital myasthenic syndromes share many of the clinical features of autoimmune myasthenia gravis. Congenital myasthenic syndromes should be suspected when symptoms of myasthenia have begun in infancy or childhood and AchR antibody tests are consistently negative.

Differential Diagnosis:

Conditions that cause weakness of the cranial or somatic musculature are;

i) Non-autoimmune Congenital Myasthenic Syndromes
ii) Drug induced Myasthenia

iii) Eaton-Lambert myasthenic syndrome

iv) Neuroasthenia

v) Hyperthyrodism

vi) Botulism

vii) Intracranial mass lesions and

viii) Progressive external ophthalmoplegia

Oropharyngeal muscle weakness causes changes in the voice, difficulty in chewing and swallowing and inadequate maintenance of the upper airway. A history of frequent choking or throat clearing or coughing after eating indicates difficulty in swallowing. Respiratory dysfunction and isolated dysphagia (without dysarthria) are rarely the initial symptoms of myasthenia gravis. There will be jaw weakness.

Weakness begins in limb or axial muscles in about 20% of MG patients[(2)]. Any trunk or limb muscle may be weak, but some are more often affected than others. Neck flexors are usually weaker than neck extensors and the deltoid, triceps and the extensors of the wrist and fingers and ankle dorsiflexors are frequently weaker than other limb muscles. Rarely, MG presents initially with focal weakness in single muscle groups, such as "dropped head syndrome" due to severe neck extensor weakness or isolated vocal cord or respiratory muscle weakness. In untreated patients with long standing disease, weakness may be fixed and severely involved muscles

may be atrophic, giving the appearance of a chronic myopathy. This is likely in muscle-specific tyrosine kinase antibody – positive myasthenia gravis.

MUSK – Antibody Myasthenia Gravis

Antibodies to Musk have been reported in upto 50% of patients with generalized myasthenia gravis who lack Ach antibodies[5] and have been recently reported in ocular myasthenia gravis as well [3,4]. The incidence of Musk-antibody myasthenia gravis is highest closer to equator and lowest closer to the poles [6]. Genetic and environmental factors play a role. MMG affects females and begins from childhood through middle age. In same, the clinical findings are indistinguishable from Anti-AchR positive MG. Many MMG patients have predominant weakness in cranial and bulbar muscles, frequently with marked atrophy of these muscles. Others have prominent neck, shoulder and respiratory weakness with little or no involvement of ocular or bulbar muscles. The electro diagnostic abnormalities may not be widespread as in other forms of MG, and it may be necessary to examine different muscles to demonstrate abnormal neuromuscular transmission [37].

Many MMG patients do not improve with cholinesterase inhibitors, some become worse and many have profuse fasciculations with these drugs[13].

Disease severity tends to be worse but most improve dramatically with plasma exchange or corticosteroids [11]. More immuno suppression is typically necessary, though long term outcome is generally good [5]. Thymic changes are absent or minimal [9,10]. The role of thymectomy in MMG is not yet clear [5, 11].

Seronegative Myasthenia Gravis:

Some MG patients lack both anti-AchR and anti-MUSK antibodies ("double seronegative MG"). They are clinically heterogenous. The true frequency of seronegative MG may be quite low.

Genetics of Myasthenia Gravis:

The family members of patients are 1000 times more likely to develop the disease than the general population. 33% to 45% of asymptomatic first degree family members show jitter on SFEMG testing and anti-AchR antibodies are slightly elevated in upto 50%. Certain HLA types (DR2, DR3, B8, DR1) predispose to MG. MMG is associated with HLA-DR14 & DQ5. In asian patients, an association of OMG with HLA-BW46 in Chinese patients have been reported [8]. Non-HLA genes are also reported to be associated with MG.

“Ice-Pack” Test

Ice Pack is applied over the drooped eyelid for 2 minutes and improvement in ptosis is assessed. Positive responses occur even when tensilon test is negative or it is contraindicated and it has a high sensitivity and specificity [7].

Treatment

There is a good prognosis in myasthenic patients and they can return to normal life after proper therapy.

The most useful treatments are

1) Anticholinesterase drugs
2) Immuno suppressive agents
3) Thymectomy
4) Plasmapheresis
5) Intravenous immunoglobulin

Anticholinestrase Drugs:

There is a partial improvement in most myasthenic patients and improvement is complete in only a few. Although, neostigmine and Pyridostigmine are the drugs useful in these patients, Pyridostigmine is most widely used drug. The beneficial action of pyridostigmine begins within 15-

30 minutes and lasts for 3-4 hours and treatment is begin with a moderate dose of 30-60mg three or four times daily. The maximum useful dose of pyridostigmine rarely exceeds 120mg every 3-6 hrs during day time. Over dosage with anticholinesterase drug may cause increased weakness and other side effects. In some patients, muscaric side effects like nausea, salivation, abdominal cramps and diarrhea may limit the dose tolerated. Atropine / diphenoxylate or loperamide are useful for these symptoms.

Thymectomy:

Thymectomy is done for surgical removal of thymoma and as a treatment of myasthenia gravis. In the absence of tumour, the evidence suggests that upto 85% of patients experience improvement after thymectomy; 35% of these achieve drug free remission [(21)]. The improvement is delayed for months to years. As a long term benefit, thymectomy diminishes or eliminates the need for continuous drug treatment. Thymectomy is indicated in all patients with generalized MG who are in the ages of puberty and upto 55 years. The recommendation of thymectomy in children, adults above 55 years of age and in patients with weakness restricted to ocular muscles in controversial. There is evidence that patients with Musk antibody postive MG may not respond to thymectomy. These is uncertainly as to whether the improvement was due to thymectomy or explicable by differences in baseline characteristics. This

will be clarified by an ongoing international prospective single blinded randomized trial of thymectomy in non-thymomatous myasthenia gravis. When there is a relapse following a response to initial surgery, repeat thymectomy can be considered. This is based on clinical suspicion [34].

Immunosuppression:

Various drugs are used for immunosuppression either in various combinations or alone.

These drugs are

1) Glucocorticoids
2) Azathioprine
3) Cyclosporine
4) Tacrolimus
5) Mycophenolate mofetil
6) High dose cyclophosphamide

Corticosteroids are the commonly used immunosuppressants in myasthenia gravis. Prednisolone causes marked improvement or complete relief of symptoms in more than 75% patients [20]. There will be transitory exacerbation of weakness in a third to half of patients who are on high dose prednisolone which begin in 7 to 10 days of starting prednisolone and lasts for several days [20]. Mycophenolate mofetil selectively blocks purine

synthesis leading to suppression of both T and B Cell proliferation. Studies indicate its efficacy in myasthenic gravis [21]. Two randomized controlled trials did not show benefit of MMF over 20mg prednisolone daily [39] and failed to show significant steroid sparing effect of MMF in those on prednisolone [22]. Tacrolimus may be effective in Myasthenia Gravis [40,17]. Cyclophosphamide administered as monthly i.v. pulse doses has been useful in severe refractory generalized myasthenia gravis. [18,19]. In a recent study, those who received immunosuppressants for minimum of 1 year, all forms benefited and the rate of remission or minimal manifestation was 85% in ocular myasthenia gravis [24]. In thymoma associated myasthenia it is 47% [32].

Plasmapheresis:

Plasma, which contains the pathogenic antibodies is mechanically separated from the blood cells which are returned to the patient. Usually five exchanges (3-4 L per exchange) is generally administered over a period of 10-14 days. It gives a short term reduction in AchR antibodies with clinical improvement. Plasmapheresis is also indicated in patients with thymoma prior to surgery to improve the patients condition.

Intravenous Immunoglobulin:

The indication for the use of IVIg are to produce a rapid improvement and also prior to thymectomy. The advantages of this immunoglobulin are that it does not require special equipment or a large bore venous access. The usual dose in 2g/kg, administered over 5 days (400 mg/kg/day). Improvement occurs in 70% of patients, beginning during treatment or within a week and continuing for weeks to months. Adverse reactions to immunoglobulin are not serious and include headache, chills, fever, fluid overload, rarely aseptic meningitis, renal failure, stroke and leukopenia. Lyophilized forms of IVIg are reported to produce increased incidence of adverse events in neuromuscular disease. Refractory exacerbations of Myasthenia Gravis can be treated with IVIg as supported by Class I evidence [(41)]. A placebo-controlled double blind recent trial showed rapid improvement in moderate to severe weakness after IVIg [(23)].

Management of Myasthenic crisis:

Myasthenic crisis is defined as a exacerbation of weakness sufficient to endanger life. It is due to respiratory failure caused by diaphragmatic and intercostal muscle weakness. Patients are to be managed in an intensive care unit. Most common cause of crisis is intercurrent infection. It should be treated with effective antibiotic therapy, respiratory assistance and pulmonary physiotherapy. Plasmapheresis or IVIg is helpful in hastening

recovery. Non-invasive mechanical ventilation with bilevel positive-pressure ventilation will avoid the need for intubation in patients in crisis without hypercapnia [28]. Retrospective studies suggest that both IVIg and plasmapheresis are equally effective in disease stabilization [26]. Other study suggest that plasmapheresis is superior in producing more rapid respiratory improvement [27].

Newer Treatments:

Anti-musk antibodies positive myasthenia gravis will improve with rituximab [5,8]. Etanercept is a recombinant human tumor necrosis factor receptor:FC. This shows improvement in myasthenia gravis [42]. Compliment inhibition is effective in experimental myasthenia gravis and clinical trials are going on in humans [43]. Autologous stem cell transplantation has been done in refractory myasthenia gravis but its role in myasthenia is unclear.

MATERIALS AND METHODS

In this open prospective study, patients admitted between 01.10.2012 and 01.12.2013 in the Neurology ward, Medical ward and IMCU of Rajiv Gandhi Government General Hospital, Madras Medical College with symptoms and signs of myasthenic crisis, fulfilling the inclusion and exclusion criterias were enrolled after explaining the study and getting consent for the study. The study was previously approved by the Institutional Ethical Committee.

Inclusion Criteria:

Patients who developed symptoms and signs of myasthenic crisis and who are admitted in Neurology ward, Medical ward and IMCU are registered for the study.

Exclusion Criteria:

1. Patients who are diagnosed to have other Medical and Surgical conditions.
2. Other co-morbid conditions like HIV, Malignancy.
3. Congenital myasthenic syndrome.
4. Renal failure

5. Hepatic failure
6. Patients with perioperative respiratory crisis associated with thymectomy.
7. Pregnant Patients :

   These patients were excluded from the study.

Methods and Analysis:

Patients with myasthenic crisis who are admitted in Neurology ward, Medical ward and IMCU were enrolled. Detailed history and physical examination findings were recorded.

All baseline investigations like Urine Routine, Complete Blood Counts, RFT, LFT were done.

X-Ray chest or CT-Chest, MRI Imaging of Brain, Brain stem and Spinal cord were done. ENMG and repetitive nerve stimulation were done in all patients. Anti-Acetyl cholinesterase and Anti-musk antibodies were measured in the blood whenever possible. Thyroid function tests were also carried out in some patients.

The following parameters are analysed:

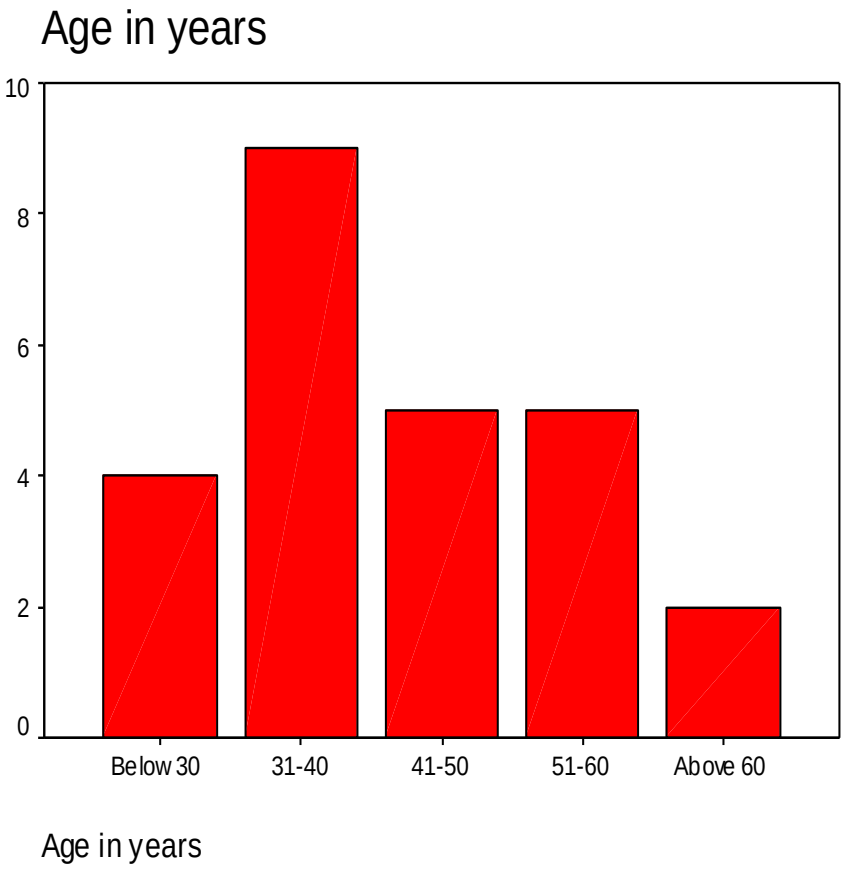
1. Demographic Data

2. Duration of illness
3. Predisposing factors
4. Clinical features
5. Associated complications
6. Duration of mechanical ventilation
7. Ventilator associated complications
8. Treatment received
9. Outcome of patients.

RESULTS & OBSERVATIONS

AGE IN YEARS

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Below 30	4	16.0	16.0	16.0
	31-40	9	36.0	36.0	52.0
	41-50	5	20.0	20.0	72.0
	51-60	5	20.0	20.0	92.0
	Above 60	2	8.0	8.0	100.0
	Total	25	100.0	100.0	

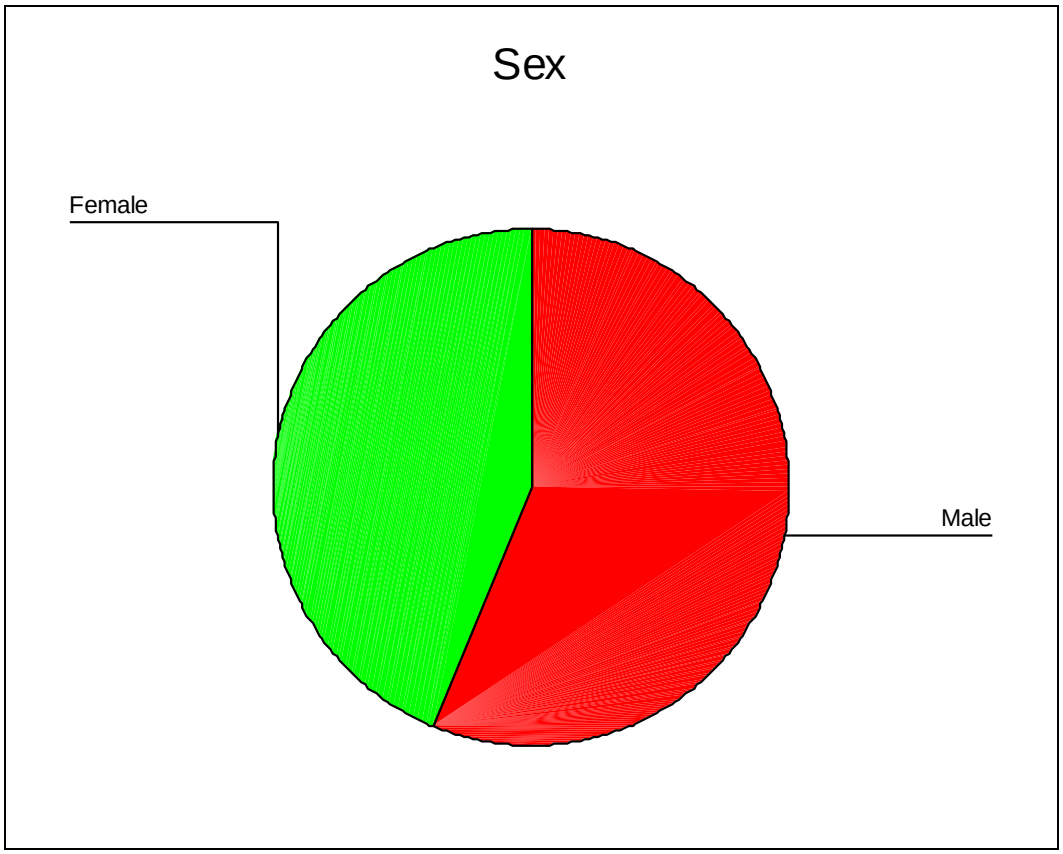


DESCRIPTIVE STATISTICS

	N	Minimum	Maximum	Mean	Std. Deviation
Age in years	25	17	65	42.08	13.086
Valid N (listwise)	25				

SEX

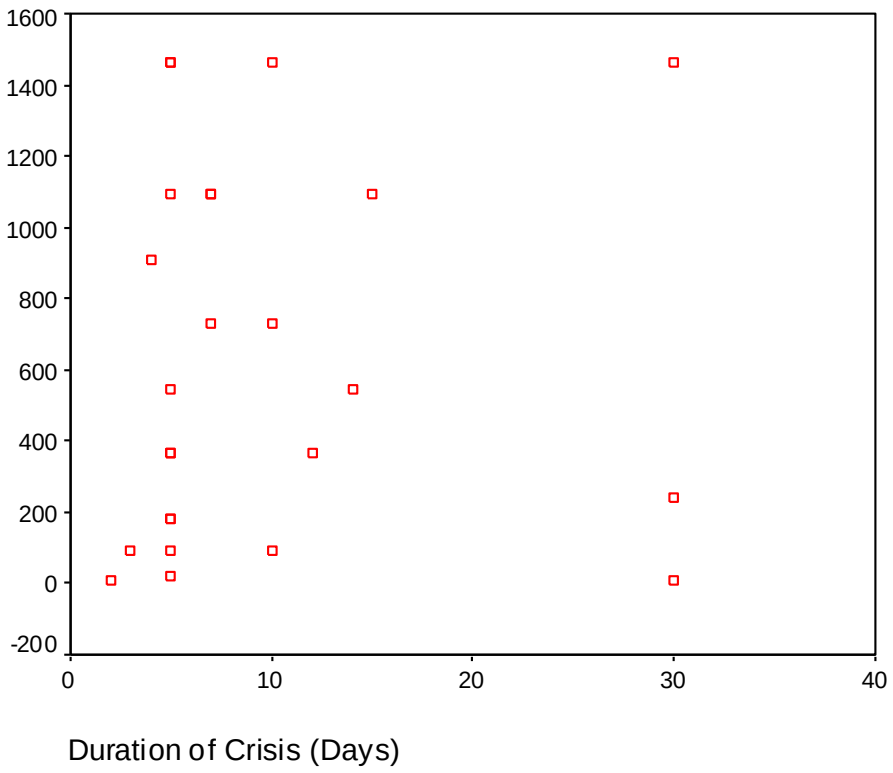
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Male	14	56.0	56.0	56.0
	Female	11	44.0	44.0	100.0
	Total	25	100.0	100.0	



Correlations

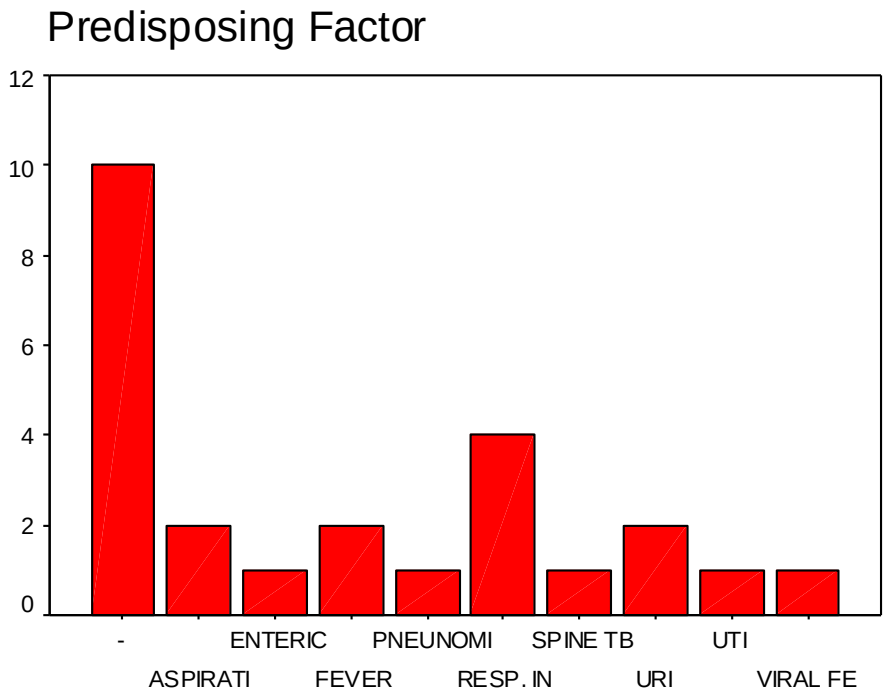
		Disease Duration (Days)	Duration of Crisis (Days)
Disease Duration (Days)	Pearson Correlation	1	.043
	Sig. (2-tailed)	.	.839
	N	25	25
Duration of Crisis (Days)	Pearson Correlation	.043	1
	Sig. (2-tailed)	.839	.
	N	25	25

Graph



PREDISPOSING FACTOR

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	-	10	40.0	40.0	40.0
	Aspirati	2	8.0	8.0	48.0
	Enteric	1	4.0	4.0	52.0
	Fever	2	8.0	8.0	60.0
	Pneunomi	1	4.0	4.0	64.0
	Resp. In	4	16.0	16.0	80.0
	Spine TB	1	4.0	4.0	84.0
	URI	2	8.0	8.0	92.0
	UTI	1	4.0	4.0	96.0
	Viral fe	1	4.0	4.0	100.0
	Total	25	100.0	100.0	



	Positive		Negative		Total	
	Count	**%**	**Count**	**%**	**Count**	**%**
Ptosis	19	76.00	6	24.00	25	100.00
Diplopia	14	56.00	11	44.00	25	100.00
Facial weakness	7	28.00	18	72.00	25	100.00
Chewing difficulty	21	84.00	4	16.00	25	100.00
Dys phagia	19	76.00	6	24.00	25	100.00
Nasal Regurgitation	12	48.00	13	52.00	25	100.00
Aspiration	3	12.00	22	88.00	25	100.00
Breath difficulty	24	96.00	1	4.00	25	100.00
Speech - Nasal	10	40.00	15	60.00	25	100.00
Speech - Dys arthric	22	88.00	3	12.00	25	100.00
Limb /Generalised weakness - Symmetric - Prox	20	80.00	5	20.00	25	100.00
Limb /Generalised weakness - Symmetric - Dist	19	76.00	6	24.00	25	100.00
Limb /Generalised weakness - Asymmetric - Prox	6	24.00	19	76.00	25	100.00
Limb /Generalised weakness - Asymmetric - Dist	5	20.00	20	80.00	25	100.00

MOTOR POWER - UL - RIGHT

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	4-	3	12.0	12.0	12.0
	4	17	68.0	68.0	80.0
	4+	2	8.0	8.0	88.0
	5	3	12.0	12.0	100.0
	Total	25	100.0	100.0	

MOTOR POWER - UL - LEFT

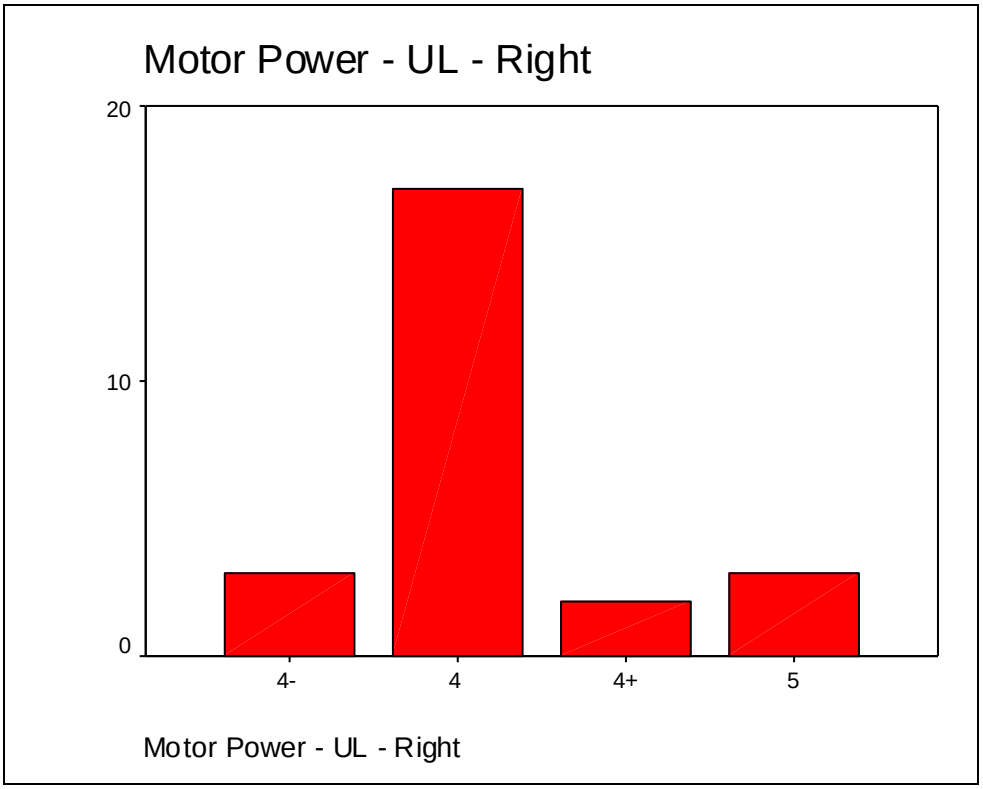
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	3	1	4.0	4.0	4.0
	4-	3	12.0	12.0	16.0
	4	16	64.0	64.0	80.0
	4+	2	8.0	8.0	88.0
	5	3	12.0	12.0	100.0
	Total	25	100.0	100.0	

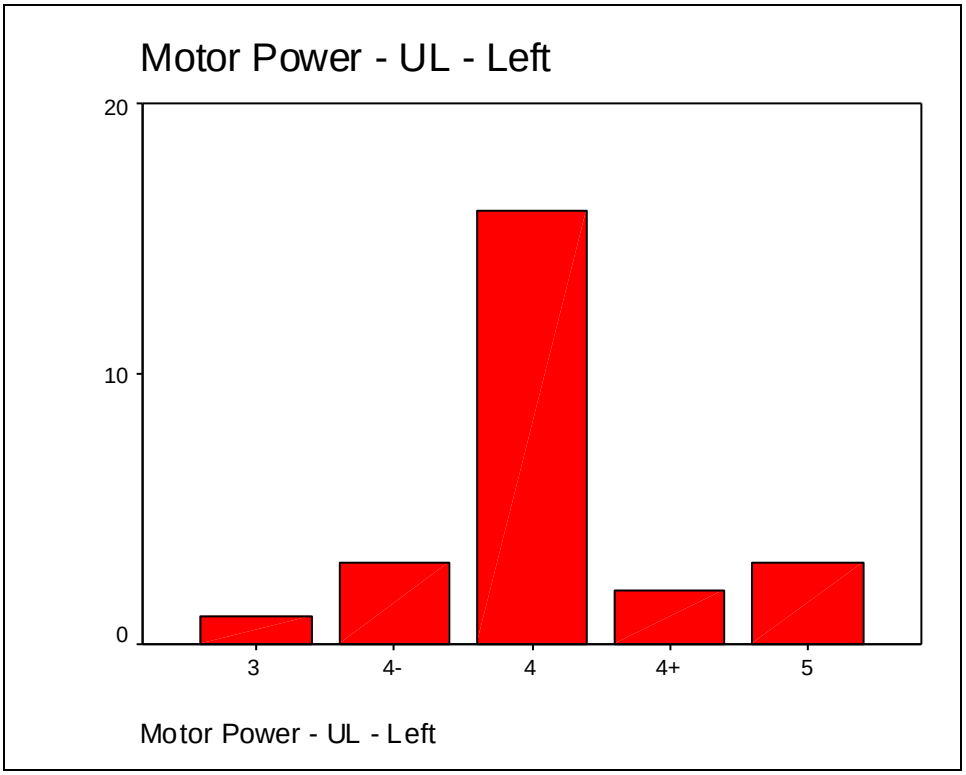
MOTOR POWER - LL - RIGHT

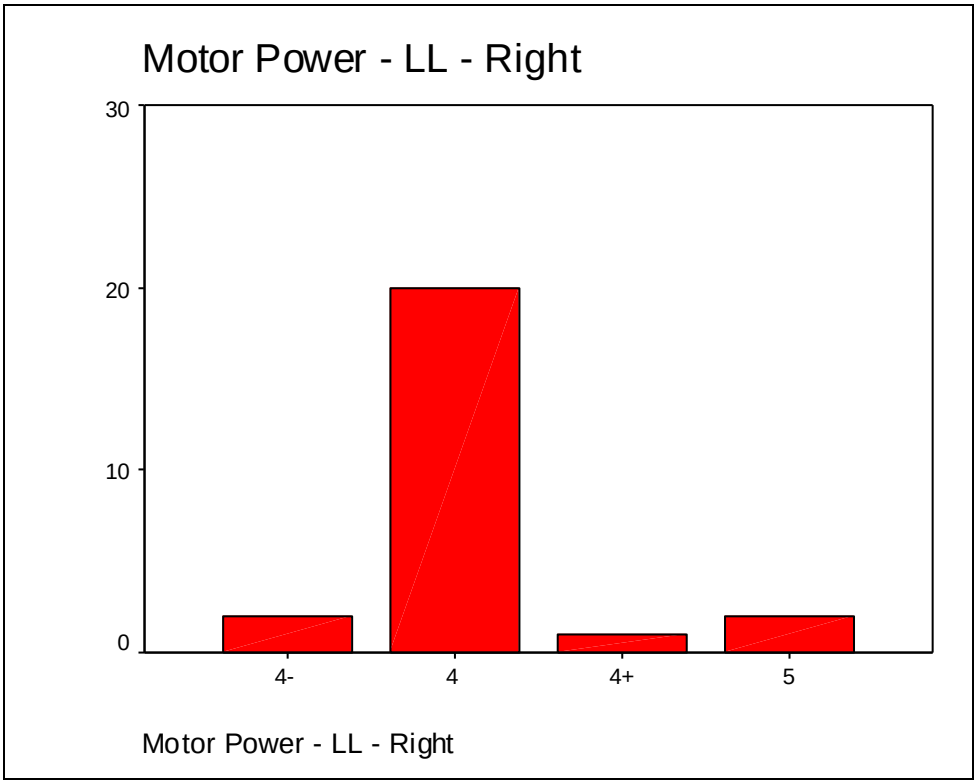
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	4-	2	8.0	8.0	8.0
	4	20	80.0	80.0	88.0
	4+	1	4.0	4.0	92.0
	5	2	8.0	8.0	100.0
	Total	25	100.0	100.0	

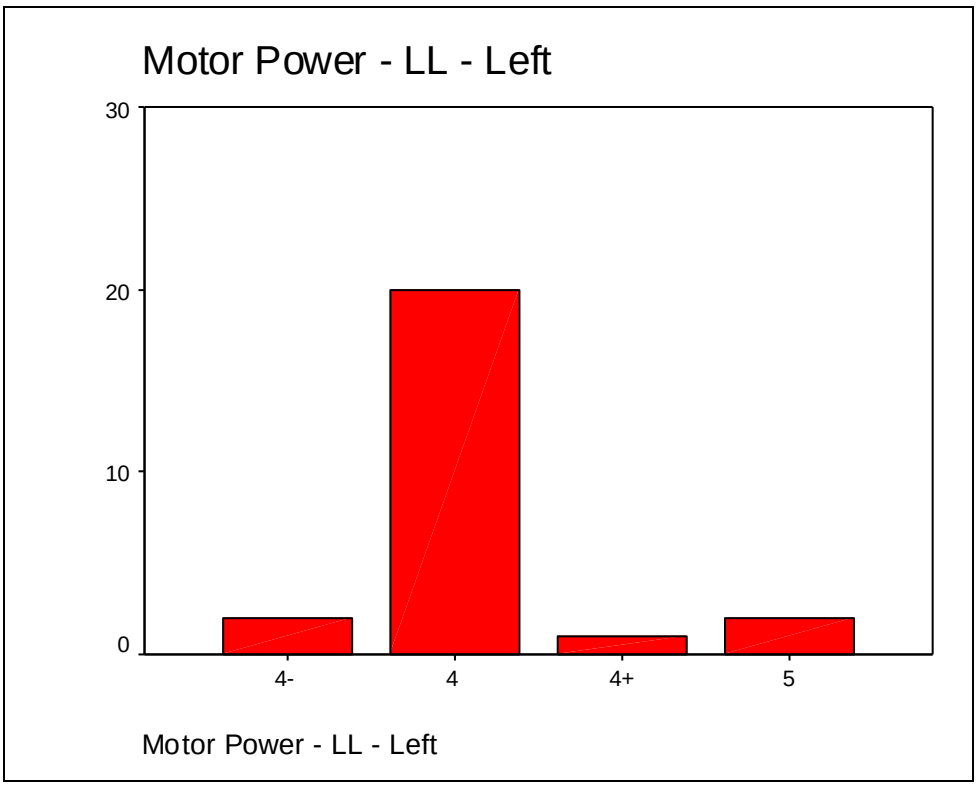
MOTOR POWER - LL - LEFT

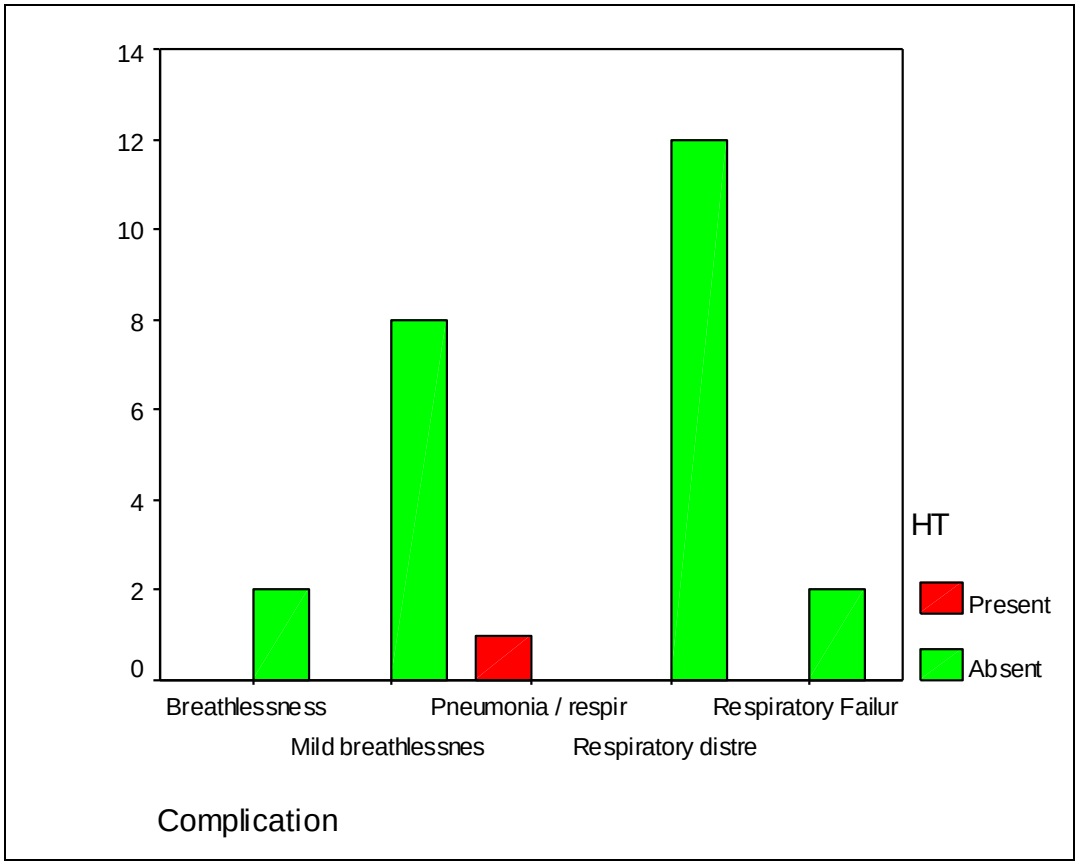
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	4-	2	8.0	8.0	8.0
	4	20	80.0	80.0	88.0
	4+	1	4.0	4.0	92.0
	5	2	8.0	8.0	100.0
	Total	25	100.0	100.0	

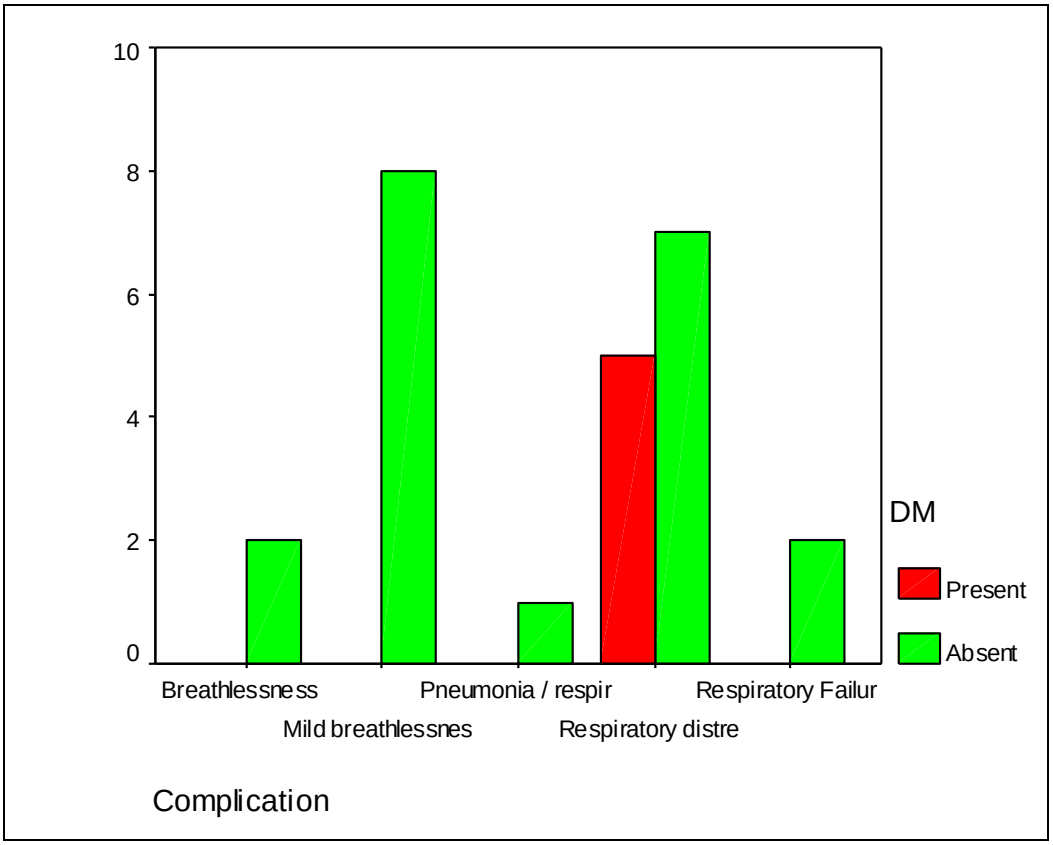

Motor Power - UL - Right
20
10
0
4-
4
4+
5
Motor Power - UL - Right


Motor Power - UL - Left
20
10
0
3
4-
4
4+
5
Motor Power - UL - Left


Motor Power - LL - Right
30
20
10
0
4-
4
4+
5
Motor Power - LL - Right


Motor Power - LL - Left
30
20
10
0
4-
4
4+
5
Motor Power - LL - Left


14
12
10
8
6
4
2
0
HT
Present
Absent
Breathlessness
Mild breathlessnes
Pneumonia / respir
Respiratory distre
Respiratory Failur
Complication

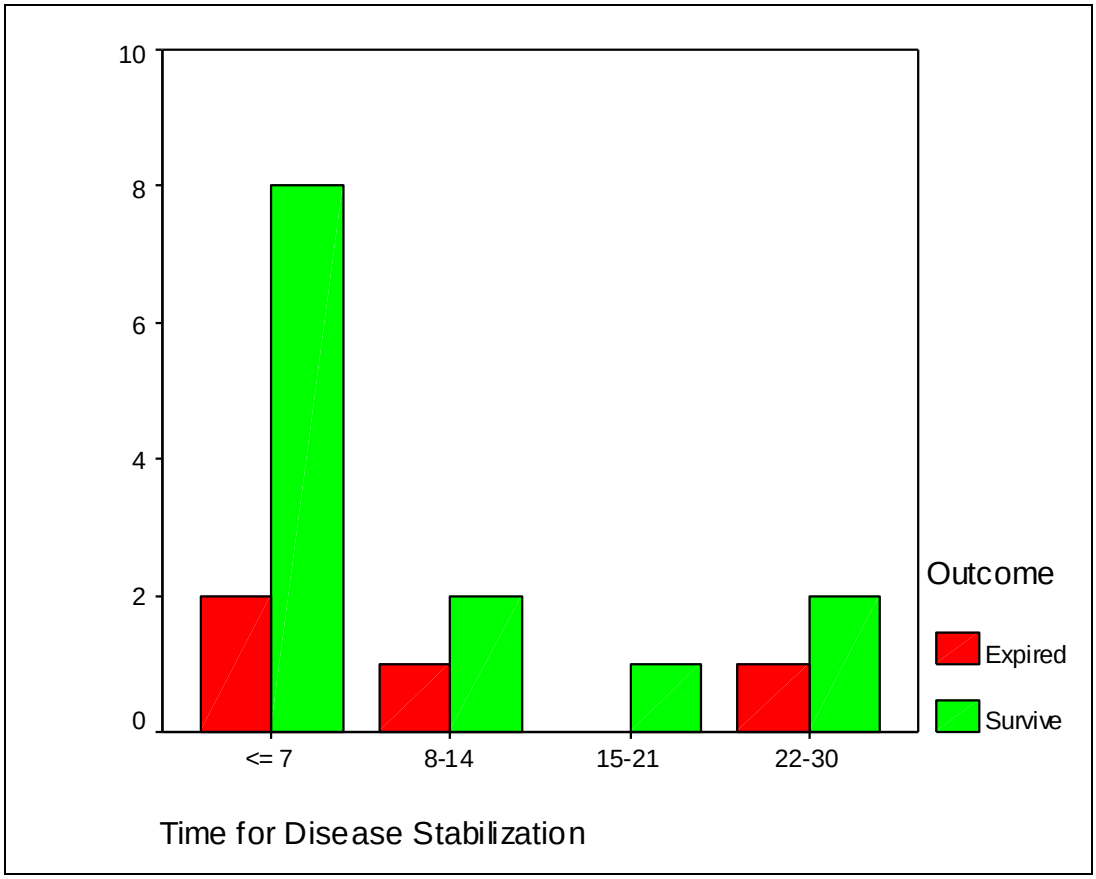

10
8
6
4
2
0
DM
Present
Absent
Breathlessness
Mild breathlessnes
Pneumonia / respir
Respiratory distre
Respiratory Failur
Complication

DESCRIPTIVE STATISTICS

	N	Minimum	Maximum	Mean	Std. Deviation
Disease Duration (Days)	25	7	1460	627.16	521.380
Interval from Sym To Crisis (Days)	25	7	1460	439.36	413.842
Duration of Crisis (Days)	25	2	30	9.64	8.336
Duration IMCU Stay (Days)	25	3	40	13.32	9.915
Valid N (listwise)	25				

TIME FOR DISEASE STABILIZATION
OUTCOME CROSS TABULATION

			Outcome		
			Expired	Survive	Total
Time for Disease Stabilization	<= 7	Count	2	8	10
		% within Time for Disease Stabilization	20.0%	80.0%	100.0%
		% within Outcome	50.0%	61.5%	58.8%
	8-14	Count	1	2	3
		% within Time for Disease Stabilization	33.3%	66.7%	100.0%
		% within Outcome	25.0%	15.4%	17.6%
	15-21	Count	0	1	1
		% within Time for Disease Stabilization	.0%	100.0%	100.0%
		% within Outcome	.0%	7.7%	5.9%
	22-30	Count	1	2	3
		% within Time for Disease Stabilization	33.3%	66.7%	100.0%
		% within Outcome	25.0%	15.4%	17.6%
Total		Count	4	13	17
		% within Time for Disease Stabilization	23.5%	76.5%	100.0%
		% within Outcome	100.0%	100.0%	100.0%

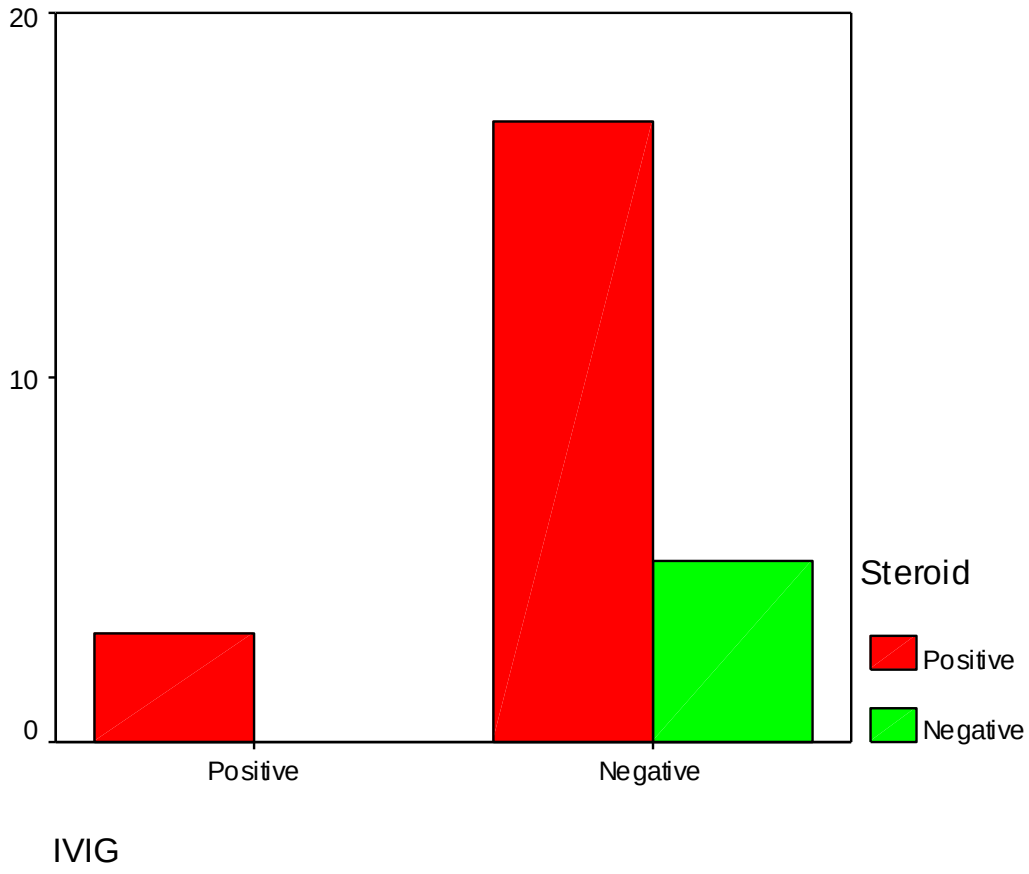

10
8
6
4
2
0
<= 7
8-14
15-21
22-30
Outcome
Expired
Survive
Time for Disease Stabilization

IVIG STEROID

			Steroid		Total
			Positive	Negative	
IVIG	Positive	Count	3	0	3
		% within IVIG	100.0%	.0%	100.0%
		% within Steroid	15.0%	.0%	12.0%
	Negative	Count	17	5	22
		% within IVIG	77.3%	22.7%	100.0%
		% within Steroid	85.0%	100.0%	88.0%
Total		Count	20	5	25
		% within IVIG	80.0%	20.0%	100.0%
		% within Steroid	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	**df**	**Asymp. Sig. (2-sided)**	**Exact Sig. (2-sided)**	**Exact Sig. (1-sided)**
Pearson Chi-Square	.852(b)	1	.356		
Continuity Correction(a)	.024	1	.878		
Likelihood Ratio	1.438	1	.230		
Fisher's Exact Test				1.000	.496
Linear-by-Linear Association	.818	1	.366		
N of Valid Cases	25				


20
10
0
Positive
Negative
IVIG
Steroid
Positive
Negative

PLASMA PHERESIS STEROID

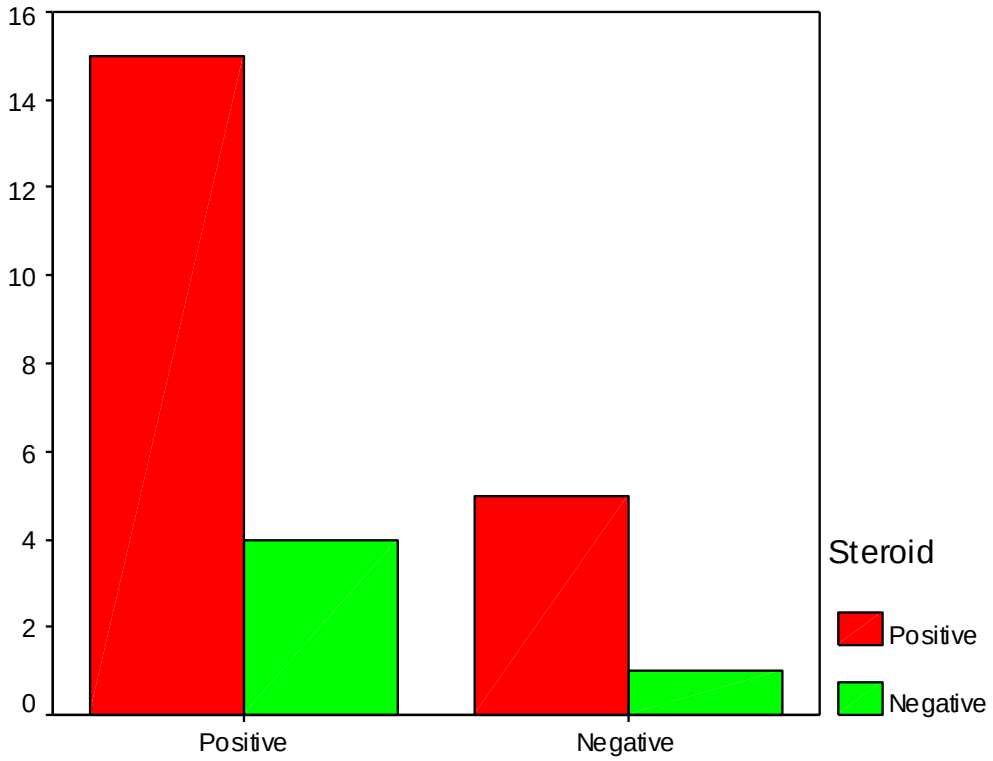
			Steroid		
			Positive	Negative	Total
Plasma Pheresis	Positive	Count	15	4	19
		% within Plasma Pheresis	78.9%	21.1%	100.0%
		% within Steroid	75.0%	80.0%	76.0%
	Negative	Count	5	1	6
		% within Plasma Pheresis	83.3%	16.7%	100.0%
		% within Steroid	25.0%	20.0%	24.0%
Total		Count	20	5	25
		% within Plasma Pheresis	80.0%	20.0%	100.0%
		% within Steroid	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.055(b)	1	.815		
Continuity Correction(a)	.000	1	1.000		
Likelihood Ratio	.057	1	.812		
Fisher's Exact Test				1.000	.657
Linear-by-Linear Association	.053	1	.819		
N of Valid Cases	25				

a Computed only for a 2x2 table

b 3 cells (75.0%) have expected count less than 5. The minimum expected count is 1.20.



IVIG

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Positive	3	12.0	12.0	12.0
	Negative	22	88.0	88.0	100.0
	Total	25	100.0	100.0	

PLASMA PHERESIS

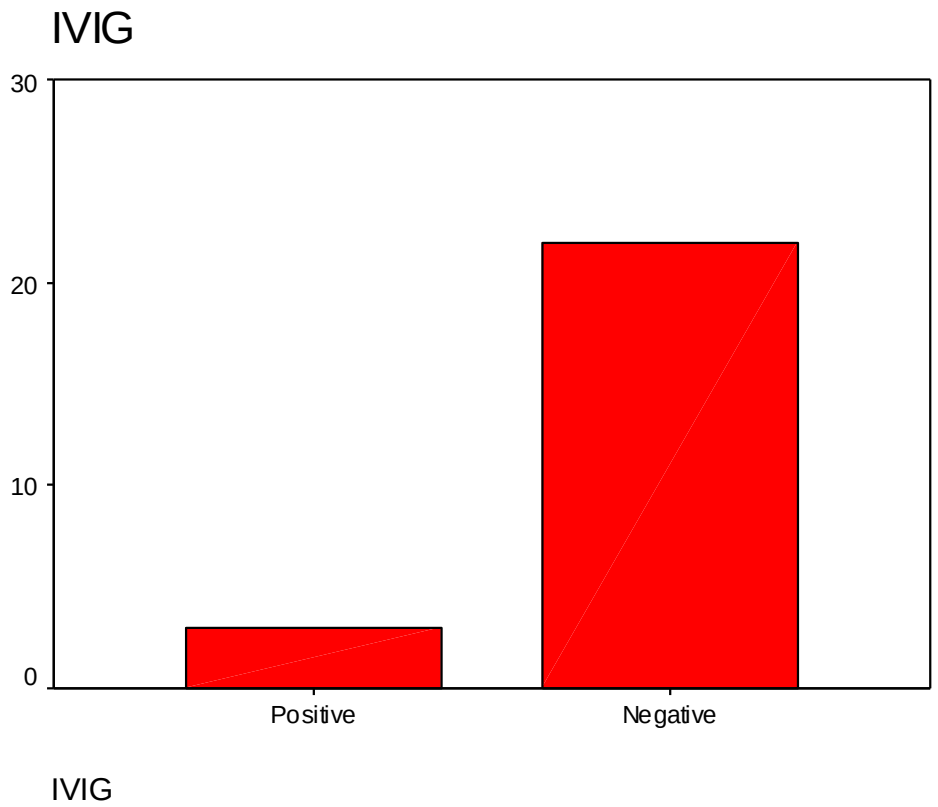
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Positive	19	76.0	76.0	76.0
	Negative	6	24.0	24.0	100.0
	Total	25	100.0	100.0	

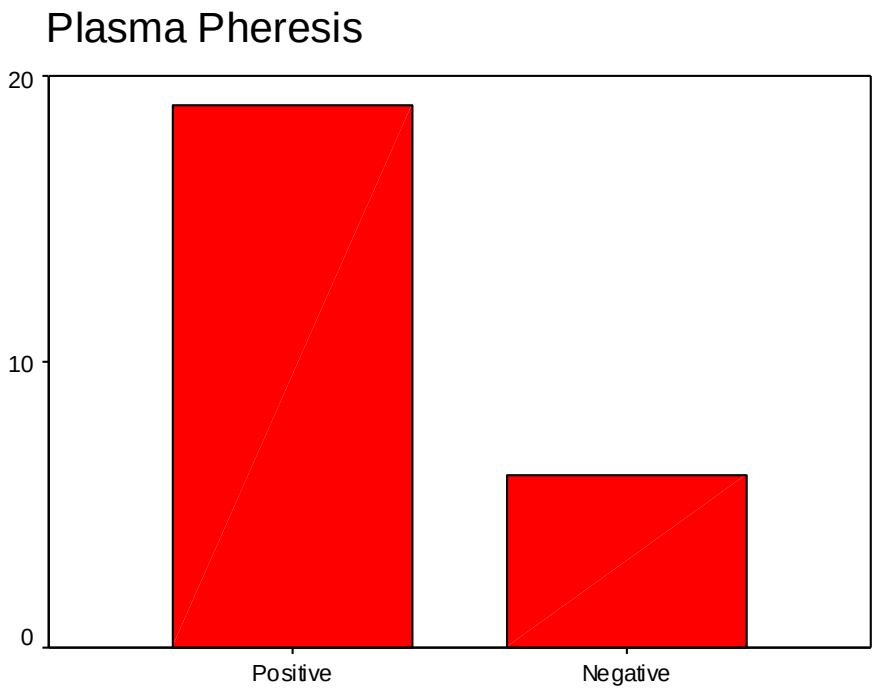
STEROID

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Positive	20	80.0	80.0	80.0
	Negative	5	20.0	20.0	100.0
	Total	25	100.0	100.0	

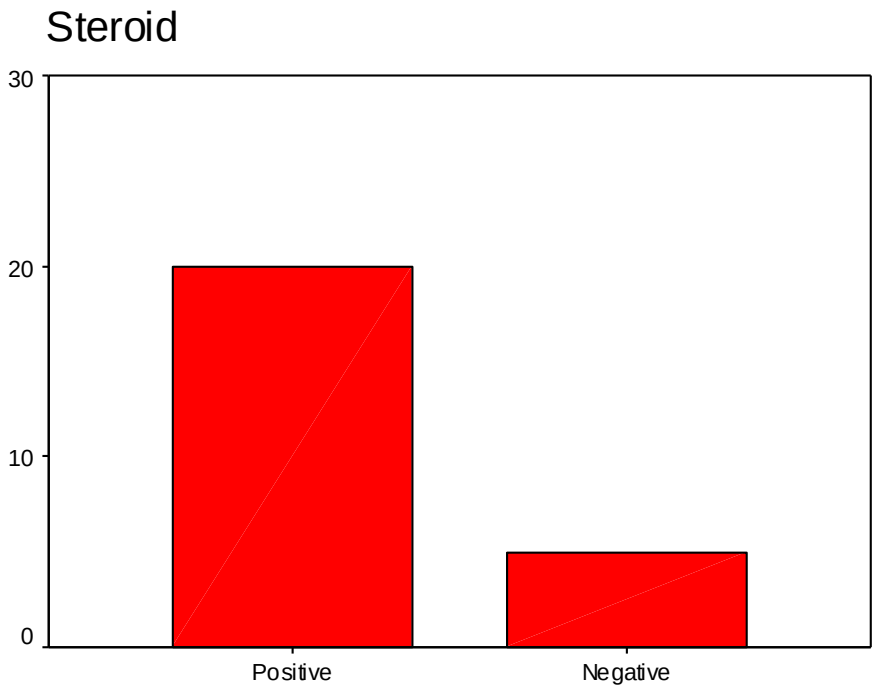
IVIG, PLASMA AND STERIOD

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Positive	24	96.0	96.0	96.0
	Negative	1	4.0	4.0	100.0
	Total	25	100.0	100.0	

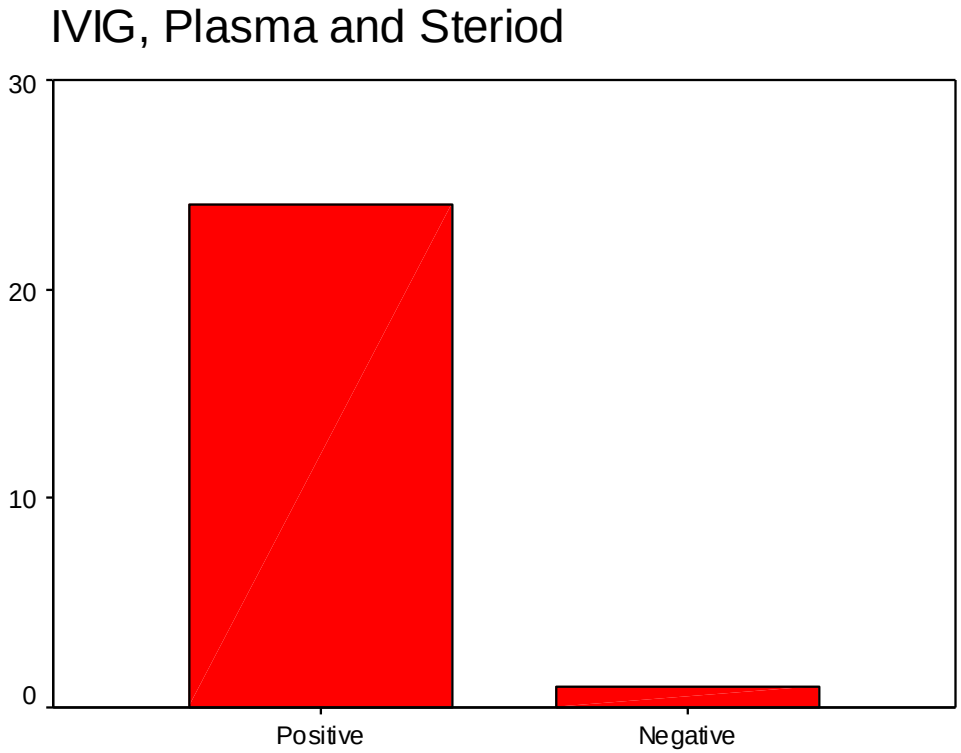




Plasma Pheresis



Steroid



IVIG, Plasma and Steriod

IVIG OUTCOME

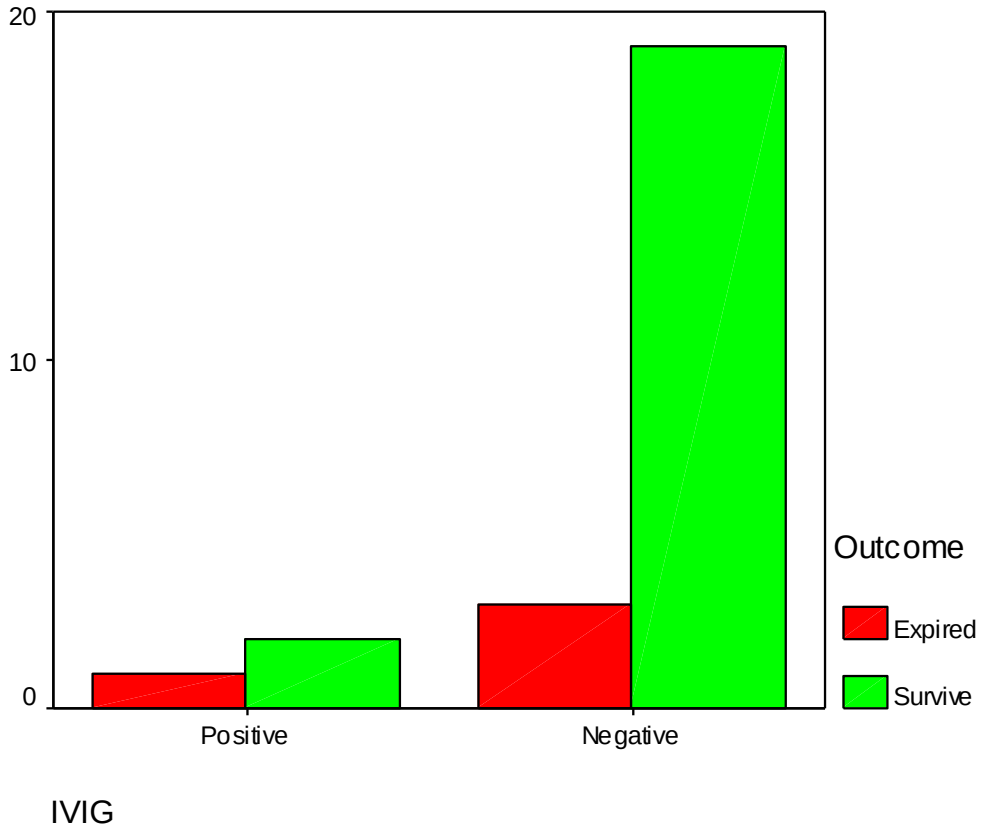
			Outcome		Total
			Expired	Survive	
IVIG	Positive	Count	1	2	3
		% within IVIG	33.3%	66.7%	100.0%
		% within Outcome	25.0%	9.5%	12.0%
	Negative	Count	3	19	22
		% within IVIG	13.6%	86.4%	100.0%
		% within Outcome	75.0%	90.5%	88.0%
Total		Count	4	21	25
		% within IVIG	16.0%	84.0%	100.0%
		% within Outcome	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.762(b)	1	.383		
Continuity Correction(a)	.001	1	.973		
Likelihood Ratio	.639	1	.424		
Fisher's Exact Test				.422	.422
Linear-by-Linear Association	.732	1	.392		
N of Valid Cases	25				

a Computed only for a 2x2 table

b 3 cells (75.0%) have expected count less than 5. The minimum expected count is .48.



PLASMA PHERESIS OUTCOME

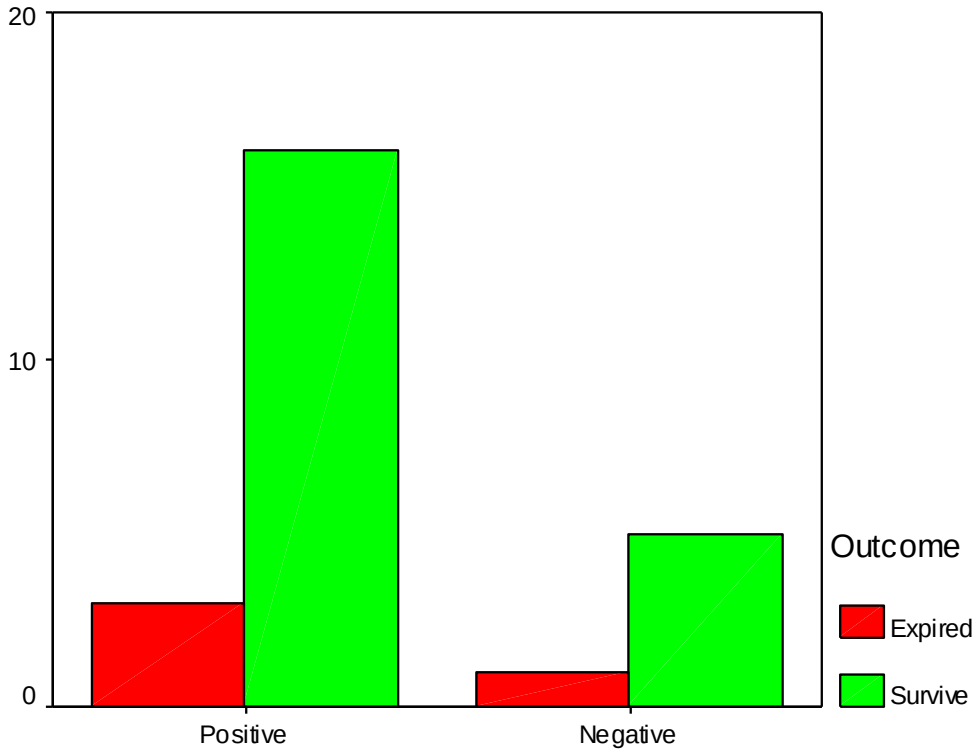
			Outcome		Total
			Expired	Survive	
Plasma Pheresis	Positive	Count	3	16	19
		% within Plasma Pheresis	15.8%	84.2%	100.0%
		% within Outcome	75.0%	76.2%	76.0%
	Negative	Count	1	5	6
		% within Plasma Pheresis	16.7%	83.3%	100.0%
		% within Outcome	25.0%	23.8%	24.0%
Total		Count	4	21	25
		% within Plasma Pheresis	16.0%	84.0%	100.0%
		% within Outcome	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.003(b)	1	.959		
Continuity Correction(a)	.000	1	1.000		
Likelihood Ratio	.003	1	.959		
Fisher's Exact Test				1.000	.694
Linear-by-Linear Association	.003	1	.960		
N of Valid Cases	25				

a Computed only for a 2x2 table

b 2 cells (50.0%) have expected count less than 5. The minimum expected count is .96.



Plasma Pheresis

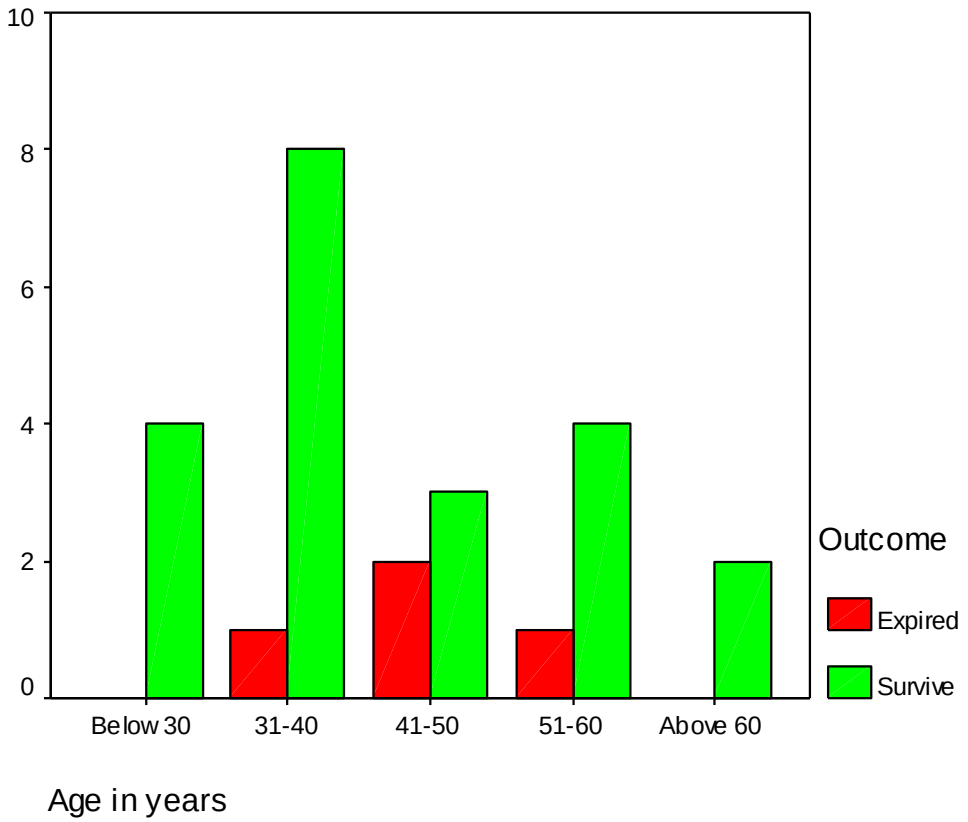
AGE IN YEARS OUTCOME CROSSTABULATION

			Outcome		
			Expired	Survive	Total
Age in years	Below 30	Count	0	4	4
		% within Age in years	.0%	100.0%	100.0%
		% within Outcome	.0%	19.0%	16.0%
	31-40	Count	1	8	9
		% within Age in years	11.1%	88.9%	100.0%
		% within Outcome	25.0%	38.1%	36.0%
	41-50	Count	2	3	5
		% within Age in years	40.0%	60.0%	100.0%
		% within Outcome	50.0%	14.3%	20.0%
	51-60	Count	1	4	5
		% within Age in years	20.0%	80.0%	100.0%
		% within Outcome	25.0%	19.0%	20.0%
	Above 60	Count	0	2	2
		% within Age in years	.0%	100.0%	100.0%
		% within Outcome	.0%	9.5%	8.0%
Total		Count	4	21	25
		% within Age in years	16.0%	84.0%	100.0%
		% within Outcome	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	**df**	**Asymp. Sig. (2-sided)**
Pearson Chi-Square	3.505(a)	4	.477
Likelihood Ratio	3.970	4	.410
Linear-by-Linear Association	.330	1	.566
N of Valid Cases	25		

a 9 cells (90.0%) have expected count less than 5. The minimum expected count is .32.



T-Test

Group Statistics

	Outcome	N	Mean	Std. Deviation	Std. Error Mean
Age in years	Expired	4	47.50	9.539	4.770
	Survive	21	41.05	13.596	2.967
Disease Duration (Days)	Expired	4	1460.00	.000	.000
	Survive	21	468.52	401.318	87.575
Duration IMCU Stay (Days)	Expired	4	12.00	12.193	6.096
	Survive	21	13.57	9.760	2.130

INDEPENDENT SAMPLES TEST

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Age in years	Equal variances assumed	1.156	.293	.900	23	.377	6.45	7.167	-8.374	21.279
	Equal variances not assumed			1.149	5.644	.297	6.45	5.617	-7.505	20.410
Disease Duration (Days)	Equal variances assumed	12.772	.002	4.856	23	.000	991.48	204.160	569.140	1413.812
	Equal variances not assumed			11.321	20.000	.000	991.48	87.575	808.799	1174.154
Duration IMCU Stay (Days)	Equal variances assumed	.385	.541	-.285	23	.778	-1.57	5.516	-12.982	9.839
	Equal variances not assumed			-.243	3.769	.820	-1.57	6.458	-19.944	16.801

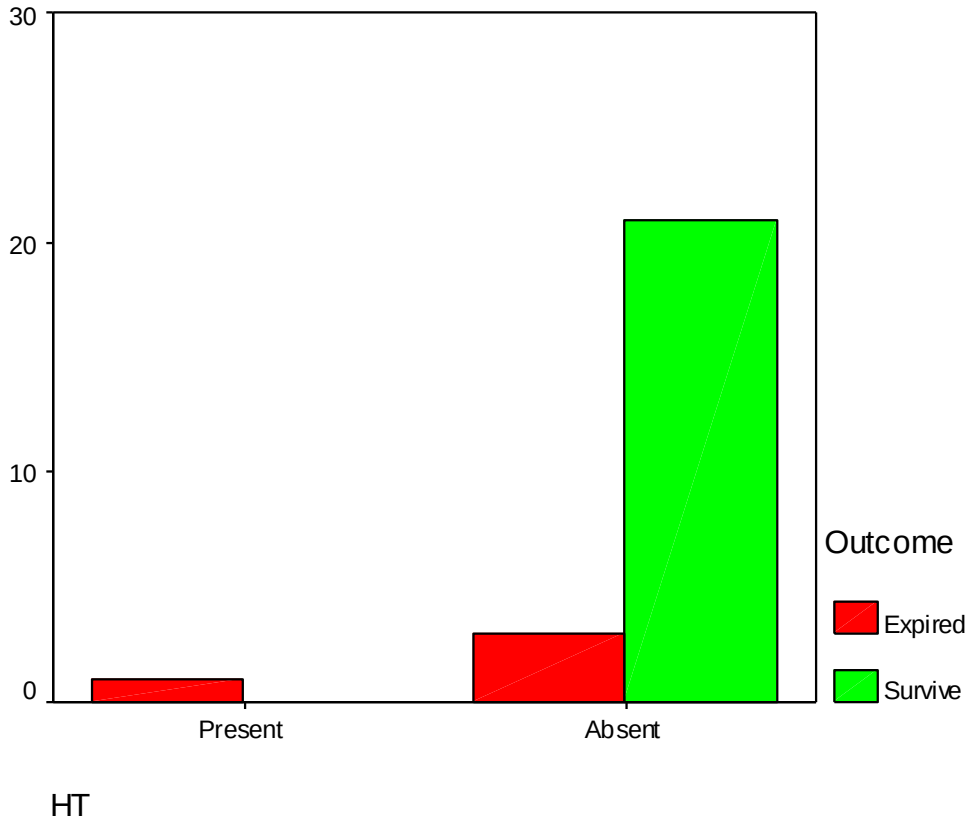
HT OUTCOME

			Outcome		
			Expired	Survive	Total
HT	Present	Count	1	0	1
		% within HT	100.0%	.0%	100.0%
		% within Outcome	25.0%	.0%	4.0%
	Absent	Count	3	21	24
		% within HT	12.5%	87.5%	100.0%
		% within Outcome	75.0%	100.0%	96.0%
Total		Count	4	21	25
		% within HT	16.0%	84.0%	100.0%
		% within Outcome	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	5.469(b)	1	.019		
Continuity Correction(a)	.896	1	.344		
Likelihood Ratio	3.899	1	.048		
Fisher's Exact Test				.160	.160
Linear-by-Linear Association	5.250	1	.022		
N of Valid Cases	25				

a Computed only for a 2x2 table
b 3 cells (75.0%) have expected count less than 5. The minimum expected count is .16.



DM OUTCOME

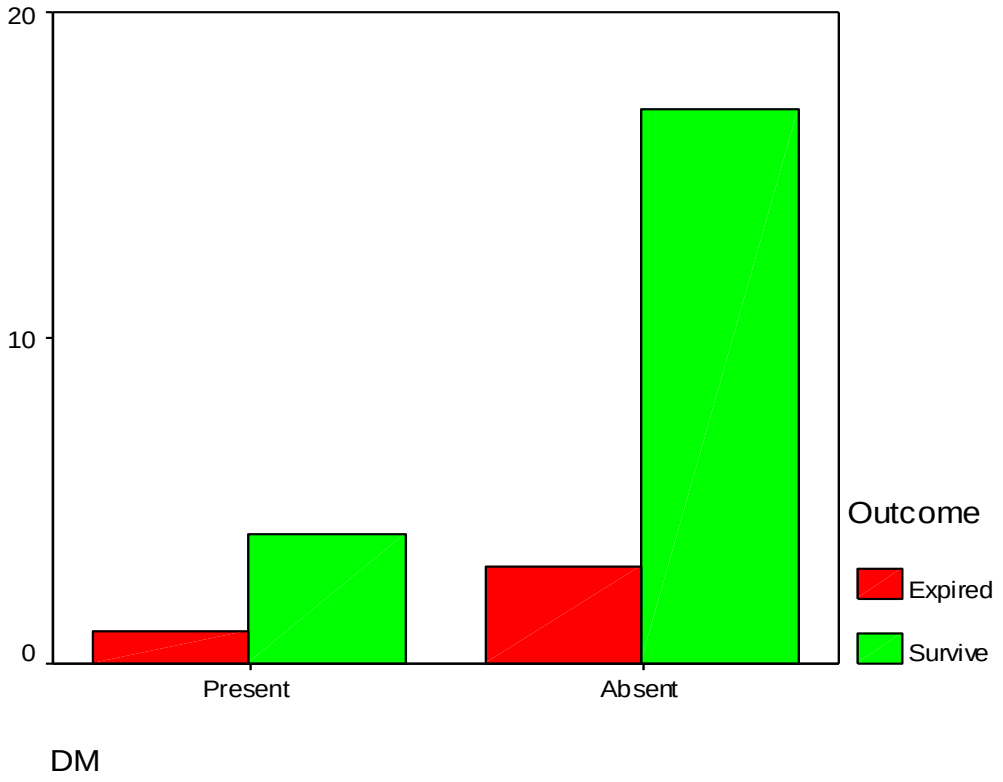
			Outcome		Total
			Expired	Survive	
DM	Present	Count	1	4	5
		% within DM	20.0%	80.0%	100.0%
		% within Outcome	25.0%	19.0%	20.0%
	Absent	Count	3	17	20
		% within DM	15.0%	85.0%	100.0%
		% within Outcome	75.0%	81.0%	80.0%
Total		Count	4	21	25
		% within DM	16.0%	84.0%	100.0%
		% within Outcome	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.074(b)	1	.785		
Continuity Correction(a)	.000	1	1.000		
Likelihood Ratio	.071	1	.790		
Fisher's Exact Test				1.000	.617
Linear-by-Linear Association	.071	1	.789		
N of Valid Cases	25				

a Computed only for a 2x2 table

b 3 cells (75.0%) have expected count less than 5. The minimum expected count is .80.



DISCUSSION

Myasthenia crisis is very often encountered in IMCU as neurological emergency. Treatment of myasthenic crisis is very cost effective as it requires ventilator support, IVIg, Plasmapheresis, technical expertise and skilled nursing care.

In our study the minimum age of onset of crisis is 17 years and maximum age of onset is 65 years. The maximum number of cases (36%) (9 patients), occurred in the age group of 31-40 with male predominance (5 males and 4 females). The mean age at presentation of crisis was 42.08 $\pm$ 13.086 [44].

Sex distribution of crisis was 56% for males (14 cases) and 44% for females (11 cases). The sex distribution and mean age of onset of crisis are similar to the study conducted at All India Institute of Medical Sciences, New Delhi [44].

Predisposing Factors:

The most common predisposing factor in our patients are respiratory infection (28%) which includes upper, lower respiratory tract infection and pneumonia. These results are comparable to that of the other studies [44,45,46]. The other predisposing factors are aspiration, tuberculosis, UTI, Enteric fever,

and viral fever. Hence adequate prevention and treatment of various infections in myasthenic patients help to reduce the incidence of crisis. Predisposing factor is the most important and independent risk factor against the duration and severity of preexisting myasthenia gravis.

Clinical Profile:

Breathing difficulty was the predominant symptom in all the patients (96%) followed by speech difficulty (88%) and chewing difficulty (84%). Limb and generalized weakness is also another predominant symptom (80%) in all the patients. Other symptoms like ptosis (76%), Dysphagia (76%), diplopia (56%), nasal regurgitation (48%) and facial weakness (28%) are in the decreasing frequency. Our patients presented with predominant bulbar symptoms similar to other studies [44,45,26].

Disease Duration and Crisis:

Our patients had a minimum disease duration of 7 days and maximum of 1460 days and a mean of 627.16 days. The interval from symptom to the onset of crisis was 7 days (minimum) and maximum of 1460 days with a mean of 439.36 days. The duration of crisis ranged from 2 to 30 days with a mean of 9.64 days. The duration of myasthenia gravis does not influence the occurrence of myasthenic crisis. Our study correlates with other studies. Three

patients presented itself with symptoms of crisis and later diagnosed to have myasthenic crisis.

Time for disease stabilization and IMCU stay:

Patients were on mechanical ventilation for a minimum of 2 days and a maximum of 30 days. 2 patients died within one week of mechanical ventilation and another patient died one week after admission but within 2 weeks. One patient died on the 30^{th} day of mechanical ventilation. Other patients improved of the symptoms. 8 patients were not intubated but were administered nasal O2 and became stable. The duration of IMCU stay also ranged from 3 days to 40 days with a mean of 13.32 days.

Complications:

Three patients developed ventilator associated pneumonia (12%). One patient developed respiratory failure, autonomic dysfunction and shock within 5 days of crisis. Another patient developed respiratory failure, pneumonia with pleural effusion and collapse of underlying lobe and pneumothorax on the opposite side with subcutaneous emphysema within 10 days of crisis. All those patients who developed VAP were on prolonged ventilation (30 days). This indicates that when patients are on ventilation for prolonged periods, they are more prone for associated complications. Comprehensive standard pulmonary

and ventilator care and hospital antibiotic usage guidelines can prevent these complications.

Thymoma and Crisis:

6 patients had thymoma. Among them 3 were operated and 3 patients were advised to undergo operation. One patient who had thymoma and on prolonged ventilation for 30 days with VAP died on the 30th day. Thymectomy was done in 5 patients with normal thymus and in 13 patients thymus was not removed. Though thymectomy was carried out on these patients, the beneficial effect of thymectomy will take longer than 1 to 2 years.

Outcome:

Higher age is a risk factor and lesser age is a favourable factor for good outcome. Duration of myasthenia gravis does not have any role on the outcome of the patient. IMCU stay is a variable factor for the outcome of myasthenic patients.

Though patients on prolonged ventilation may be prone for VAP and other ventilator related complications, the better survival rate in ventilated patients outweigh the preventable ventilator related complications. Commonly in olden days, co-morbid conditions have a major negative impact on the outcome of the myasthenia crisis.

Standardised myasthenia crisis treatment protocol and advanced ICU care setup minimizes the negative impact of the co-morbid conditions on myasthenic crisis. The therapeutic regimen should be tailored to the patients age, severity of crisis, circulatory status and comorbid conditions. Fixed standardized and combined treatment regimen is not suitable for each and every patient. As the sample size is very small, it needs further study.

CONCLUSION

1. In our study, the commonest age group of presentation of myasthenic crisis is the fourth decade (36%).
2. Male predominance (56%) was noted in our study.
3. The most common predisposing factor is the respiratory infection (28%).
4. In three patients, the presenting symptoms of myasthenia gravis was crisis itself.
5. The mean duration of onset of myasthenia gravis to the onset of crisis was 439.36 days.
6. The duration of myasthenia gravis does not influence the occurrence of myasthenic crisis.
7. Our patients presented with predominant bulbar symptoms with respiratory distress.
8. Ventilator associated pneumonia and other respiratory complications influenced the outcome of treatment of myasthenic crisis.
9. 32% of thymectomised patients had myasthenic crisis.
10. Higher age is a risk factor and younger age is a favourable factor for good outcome.
11. Duration of myasthenia gravis have no role on the outcome of crisis.
12. The better survival rate in ventilated patients outweigh the preventable ventilator related complications.

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PROFORMA

Name : Age : Sex :

Address : Unit : Ward :

Present History:

Symptoms: **Duration:**

Ptosis :

Diplopia :

Facial Weakness :

Chewing Difficulty :

Dysphagia :

Nasal Regurgitation :

Aspiration :

Breathing Difficulty :

Speech Difficulty :

Limb or Generalized Weakness:

Past History:

Diabetes Mellitus :

Hypertension :

Tuberculosis :

Hepatitis :

Renal Disease :

Glaucoma :

Respiratory Infection :

Thyroid Disorder :

Autoimmune Disorder:

Personal History

Smoking :

Alcohol Consumption :

Physical Examination:

Fever :

Anaemia :

Jaundice :

Tuberculosis Stigmata :

Pedal Oedema :

Neck Swelling :

Vitals:

Pulse : BP : Body Temperature :

Neurological Examination:

Consciousness

Cranial Nerve Examination:

Power : **Neck**

Right Upper Limb Left Upper Limb

Right Lower Limb Left Lower Limb

Trunk Muscle Power

Other System Examination

Laboratory Parameter

Complete Blood Count :

Blood Sugar :

Blood Urea :

Serum Creatinine :

Serum Electrolytes :

Liver Function Tests :

Anti Ach-R Antibody :

Anti Musk Antibody :

Repetitive Nerve Stimulation :

CT or MRI Brain :

X-ray Chest (or) CT-Chest :

MASTER CHART 1

S. No	Age	Sex	Demography	Illness Duration (Days)	Symptoms										Limb weakness /Generalised weakness				
					Ptosis	Diplopia	Facial weakness	Chewing difficulty	Dys phagia	Nasal Regurgitation	Aspiration	Breath difficulty	Speech		Symmetric		Asymmetric		
													Nasal	Dys arthric	Prox	Dist.	Prox	Dist.	
1	43	F		7		+		+		+	+	+	+		+	+	+	+	
2	38	F		1095	+				+	+		+	+	+					Precipating factor fever 3 days burning micturition = UTI Quantitative score on admission = 25/39 Discharge = 10/39
3	35	M		90	+	+		+	+				+	+	-	-	-	-	Thymectomy done on 14.02.14 ocular myasthenia detected on 15.01.14
4	48	M		1460	+	+	+	+	+	+		+	+	+	+	+	+	+	Orbicularis oculi / oris = weak Buccinator neck flexor - weak
5	27	M		545		+	+	+	+			+	+	+					Orbicularis oculi / oris = weak Masseter Neck-flex ext. / weak
6	19	M		90	+	+		+	+			+							enteric fever 5 days, following which developed symptoms
7	31	M		20					+	+		+	+	+					
8	63	F		1095								+			+	+	+	+	
9	51	M		7	+			+	+			+	+	+	+	+			
10	45	F		180	+	+	+	+		+		+	+	+	+	+	+	+	Orbicularis oculi/oris weak Nasolabial fold-obliterated bil. Nasal regurgitation with bulbar symptoms-15 days
11	32	M		730	+	-	-	+	-	+	-	+	-	+	+	+	-	-	Slurring of speech, Dournal variation of weakness+, Thymectomy done 10 months back
12	34	M		730	+	+		+	+	+		+	+	+	+	-	+	-	Neck flexion & extension = weak Trunk muscle-weak

S. No	Age	Sex	Demography	Illness Duration (Days)	Symptoms										Limb weakness /Generalised weakness				
													Speech		Symmetric		Asymmetric		
					Ptosis	Diplopia	Facial weakness	Chewing difficulty	Dys phagia	Nasal Regurgitation	Aspiration	Breath difficulty	Nasal	Dys arthric	Prox	Dist.	Prox	Dist.	
13	45	M		545	+			+	+	+		+		+	+	+	-	-	
14	17	M		365	+	+	-	+	+	-		+		+	+	+	-	-	
15	30	F		910	+			+	+			+		+	+	+	-	-	
16	58	F		1095	+	Mild bluring	-	+	+	-	-	+	-	+	+	+	-	-	
17	54	M		365	+	-		+	+			+		+	+	+	-	-	
18	39	F		180		+	+	+	+			+		+	+	+	-	-	
19	60	M		365	+			+	+	+	+	+		+	+	+	-	-	
20	36	F		90	+			+	+			+		+	+	+	-	-	
21	65	F		240	+	+	+	+	+	+		+		+	+	+	-	-	
22	37	F		1460	+	+						+		+	+	+	-	-	
23	60	M		2190	-	-	-	+				+		+	+	+	-	-	
24	45	F		1460	+	+	+	+	+	+	+	+	+	+	+	+	-	-	
25	40	M		1095	+	+	+	+	+	+		+		+	+	+	+	+	

S. No	Age	Sex	Signs											
			Ptosis	EOM	V	VII	IX&X	Tongue Weakness	Motor Power				Trunk Muscle Weakness	Respiratory Muscle Weakness
									UL		LL			
									RT	LT	RT	LT		
1	43	F		Restriction		Bil +	Palatal move ↓	-	4-	4-	4	4		+
2	38	F	+	-				-	5	5	5	5		
3	35	M	+				Palatal move ↓	-	5	5	5	5	-	-
4	48	M	+	Restriction			Palatal move ↓		Prox 3 Distal 4+	Prox 3 Distal 4+	Prox 3 Distal 4	Prox 3 Distal 4	Neck flexor-weak	
5	27	M	+	Restriction		Bil +			Prox & distal 4	4	4	4	Neck flexor-weak Neck Extensor weak	
6	19	M	+	Restriction			Palatal move ↓	-						
7	31	M				Bil +	Palatal move ↓	-	Pr-4+ Dis-5	Pr-4+ Dis-5	Pr-4+ Dis-5	Pr-4+ Dis-5		
8	63	F	+				Palatal move ↓		Pr-4 Dis-4+	Pr-4 Dis-4+	Pr-4 Dis-4+	Pr-4 Dis-4+		
9	51	M	+				Palatal move ↓		Pr-4 Dis-4+	Pr-4 Dis-4+	Pr-4 Dis-4+	Pr-4 Dis-4+		
10	45	F	+	Restriction			Palatal↓ Gag↓ Vulva mov ↓		4+	4+	4+	4+		
11	32	M	+						Pr-4- Dis-4-	Pr-4- Dis-4-	Pr-3 Dis-4	Pr-3 Dis-4		
12	34	M	+	Restriction	(+) jaw drop		Palatal move ↓		Pr-4 Dis-4+	Pr-4 Dis-4+	Pr-4 Dis-5	Pr-4 Dis-5	+	+

S. No	Age	Sex	Signs											
			Ptosis time	EOM	VN	VII	IX&X	Tongue Weakness	Motor Power				Muscle trunk weak	Resp mus weak
									UL		LL			
									RT	LT	RT	LT		
13	45	M	+				Palatal move ↓		4	4	4	4	+	+
14	17	M	+	Restriction			Palatal move ↓		4	4	4	4		
15	30	F	+	Restriction			Palatal move ↓		4	4	4	4		
16	58	F	+	Restriction			Palatal move ↓		4	4	4	4		
17	54	M	+				Palatal move ↓		4	4	4	4		
18	39	F	-	Restriction	+	+	Palatal move ↓	-	4	4	4	4	+	+
19	60	M	+	Restriction			Palatal move ↓		4	4	4	4	+	+
20	36	F	+				Palatal move ↓		4	4	4	4		
21	65	F	+	Restriction		+	Palatal move ↓		4-	4-	4-	4-	+	+
22	37	F	+	Restriction	-	-	-	-	4	3	4	4	+	
23	60	M		-	-	-			1 3	1 3	1 3	1 3		
24	45	F	+	Restriction	+	+	Palatal move ↓	-	4-	4-	4-	4-		
25	40	M	+	Restriction			Palatal move ↓		4- 4	4- 4	4- 4	4- 4	+	+

S. No	Age	Sex	Co-Morbid Conditions												Treatment for Other Conditions	Complication	Mechanical Ventilation duration (Days)
			HT	DM	Renal Disease	Glaucoma	TB	Hepatitis	Resp. Infection	Others	Thymoma	Thyroid		Auto Immune Disorder			
												Hypo	Hyper				
1	43	F					spinal + TB		+		NEG	Nodular colloid goitre			Thymectomy done	Resiratory diseases	30
2	38	F		+							NEG					Respiratory distress	15
3	35	M									NEG	-	-	-	Thymectomy done	Mild breathlessness	Nasal02
4	48	M		+							NEG					Respiratory distress	30
5	27	M		+						Viral Fever +	+					Respiratory distress	5
6	19	M								Enterir Fever +	NEG					Respiratory distress	5
7	31	M									NEG					Respiratory distress	5
8	63	F		+							NEG			RA +VE		Respiratory distress	7
9	51	M									+				Thymectomy done	Respiratory distress	2
10	45	F									NEG					Mild breathlessness	Nasal02
11	32	M									NEG				Thymectomy done	Mild breathlessness	Nasal02
12	34	M									NEG				Thymectomy done	Respiratory distress	7

S. No	Age	Sex	Co-Morbid Conditions												Treatment for Other Conditions	Complication	Mechanical Ventilation duration (Days)
			HT	DM	Renal Disease	Glaucoma	TB	Hepatitis	Resp. Infection	Others	Thymoma	Thyroid		Auto Immune Disorder			
												Hypo	Hyper				
13	45	M							+		NEG					Respiratory distress	14
14	17	M							+		+					Mild breathlessness	Nasal 02
15	30	F							+		+					Mild breathlessness	Nasal 02
16	58	F							URI		NEG					Mild breathlessness	Nasal 02
17	54	M								fever	+					Mild breathlessness	Nasal 02
18	39	F	-	-	-	-	-				NEG					Breathlessness	5
19	60	M	-	+							NEG					Respiratory distress	12
20	36	F							+		NEG					Mild breathlessness	Nasal 02
21	65	F								Fever	NEG					Respiratory distress	30
22	37	F						HBsAg +ve			NEG					Respiratory Failure	3
23	60	M	+						Fever with chills20 days, Loose stools 15 days, Followed by weakness of all 4 limbs over 20 days. Pneumonia		NEG					Pneumonia / respiratory failure	5
24	45	F									NEG					Respiratory failure, Lt. pleural effusion with consolidation and collapse of Lt. lower lobe, Rt. Pneumothorax with subcutaneous Emphysema	8
25	40	M							URI		+					Breathlessnes	7

S. No	Age	Sex	Ventilator associated complication	Investigations				RNS	CT or MRI Brain	X-Ray Chest or CT-Chest
				Blood Count	Blood Sugar	Ach-R Antibody	Anti-Musk Antibody			
1	43	F	Ventilator associated pneumonia	N	N	-	-	Decremental Response	CT Brain - N	X-ray Chest-N, ECG -N, USG-N, Tracheal culture - pseudomonas, Catheter Tip - Proteus mirabilis
2	38	F		N	N	-	-	No decremental response; pt. on drug		CT Chest-N, ECG-N, X-ray Chest-N, ECHO-N
3	35	M		N	N	-	-	Decremental Response	CT-Brain-N	CT-Chest-N, ECG-N, X-ray Chest-N, ECHO-N Blood & Urine Culture - N MSAT, Widal, Dengue - Neg
4	48	M	VAP	N	↑	-	-	Decremental Response	CT-Brain-N	X-ray chest- upper mediastinal widening +, ECG-N, ECHO-N, Urine Culture-N, Tracheal culture-Pseudomonas
5	27	M	-	N	N	17.9 nmol/L	-	Decremental Response	CT-Brain-N	CT-Chest-Moderate Sized hetegenously enhancing soft tissue lesion with calcification in Ant-mediastinum S/o. Thymoma, MP:MF-N, Msat Lepto-N, ECG-N, M.Widal-N, Mild bilirubin- ↑, HIV Elisa-N
6	19	M	-	N	N	-	-	Decremental Response	CT-Brain-N	CT-Chest - No thymus, HIV-N, VDRL-N Thyroid Profile - N
7	31	M	-	N	N	↑	-	Decremental Response	CT-Brain-N	CT-Chest-N, ECG-n, ECHO-N, HIV-N, LFT-N, Lipid Profile-N, Thyroid Profile-N
8	63	F	-	N	↑	-	-	Decremental Response	CT-Brain-N	Thymectomy Done, ECG-N, CV-Doppler-N, ECHO-N, Lipid Profile-N, RF-Pos, CRP-↑
9	51	M	-	N	N	-	-	Decremental Response	CT-Brain-N	CT-Chest, Nodular lesion Lt. lobe of thymus, Thymectomy done
10	45	F	-	N	N	-	-	Decremental Response	CT-Brain-N	X-Ray Chest-N, ECG-N, RFT, LFT-N
11	32	M	-	N	N	-	-	Decremental Response	CT-Brain-N	-
12	34	M	-	N	N	13.40 nmol/L	-	Decremental Response	Normal	X-ray chest-Normal Thyroid profile=Normal

S. No	Age	Sex	Ventilator associated complication	Investigations				RNS	CT or MRI Brain	X-Ray Chest or CT-Chest
				Blood Count	Blood Sugar	Ach-R Antibody	Anti-Musk Antibody			
13	45	M	-	N	N			Decremental response	Normal	N
14	17	M	-	N	N	-	-	Decremental response	Normal	S/o. Thymoma ; advised thymectomy
15	30	F	-	N	N	-	-	Decremental response	Normal	S/o. Thymoma ; advised thymectomy
16	58	F	-	N	N	-	-	Decremental response	Normal	Normal
17	54	M	-	N	N	-	-	Decremental response	Normal	S/o. Thymoma
18	39	F	-	N	N	-	-	Decremental response	Normal	X-ray chest = Normal RFT = Normal, LFT = Normal
19	60	M	-	N	N	-	-	Decremental response	Normal	X-ray chest = Normal RFT = Normal
20	36	F	-	N	N	-	-	Decremental response	Normal	
21	65	F	VAP	N	N	-	-	Decremental response	Normal	X-ray chest - Normal
22	37	F	-	N	N	-	-	Decremental response	Normal	X-ray chest - Normal
23	60	M	-	N	N	-	-	Decremental response	Normal	X-ray chest - Normal
24	45	F	-	N	N	-	-	Decremental response	Normal	X-ray chest & CT Chest - Lt. effusion with consolidation & collapse of Lt. Lower lobe, Rt. Pneumothorax with subcutaneous emphysema.
25	40	M	-	N	N	pos	-	Decremental response	Normal	X-ray chest S/o. thymoma

S. No	Age	Sex	Treatment Given							Outcome
			Acetylcholine esterase inhibitor	Steroid	Thymectomy	Immuno suppressive drug	Antibiotics	IVIg	Plasmapheresis	
1	43	F	pyridostigmine, neostigmine	Prednisolone	Done		+	5 doses given	5 cycles given	After improvement of bulbar & limb weakness, thymectomy done
2	38	F	neostigmine	Prednisolone	-	-	+	-	-	Rt. Feeding Improved
3	35	M	pyridostigmine	Prednisolone	Done	Azathioprine	+	-	5 cycles given	Symptoms improved
4	48	M	pyridostigmine	Prednisolone	-	-	+	5 doses	5 cycles given	pt. showed initial improvement - later deteriorated - died after a stay of 1 month
5	27	M	pyridostigmine, neostigmine	Inj. Decadran T.Prednisolone	Done	Azathioprine	+	-	5 cycles given	Improved
6	19	M	pyridostigmine	Prednisolone	-	-	+	-	-	Improved
7	31	M	pyridostigmine	Prednisolone	-	-	-	-	-	Improved
8	63	F	pyridostigmine		Done	Azathiopine	+	-	5 cycles given	Improved
9	51	M	pyridostigmine, neostigmine	Prednisolone	Done	Azathiopine	+	-	-	Improved
10	45	F	pyridostigmine	Prednisolone	-	-	+	-	-	Improved
11	32	M	pyridostigmine	Predmisolone	Done	Azathiopine	-	-	5 cycles given	Improved
12	34	M	T.Pyridostigmine T.Neostigmine	Predmisolone	Done June2013 Thymoma B3 type Stage I symptom free for 1 yr	Azathioprine Mycophenolate moefetil	+	+	thrice each time 5 cycles	Refractory to AchR esterase inhibitors and immuno suppressants. AchR antibody +ve M.G.

S. No	Age	Sex	Treatment Given							Outcome
			Acetylcholine esterase inhibitor	Steroid	Thymectomy	Immuno suppressive drug	Antibodies	IVIg	Plasmopheresis	
13	45	M	Pyridostigmine	prednisolone			+	-	5 cycles given	Improved
14	17	M	Pyridostigmine	prednisolone	advised	-	+	-	5 cycles given	Improved
15	30	F	pyridostigmine	Prednisolone	advised	-	+	-	5 cycles given	Improved
16	58	F	pyridostigmine	Prednisolone	-	-	+	-	5 cycles given	Improved
17	54	M	pyridostigmine	Prednisolone	Done	-	+	-	5 cycles given	Improved
18	39	F	pyridostigmine	Prednisolone	-	-	+	-	-	Improved
19	60	M	pyridostigmine	Prednisolone	-	-	+	-	5 cycles given	Improved
20	36	F	pyridostigmine	Prednisolone	-	-	+	-	5 cycles given	Improved
21	65	F	pyridostigmine	Prednisolone	-	-	+	-	5 cycles given	Improved
22	37	F	pyridostigmine	Prednisolone	-	Azathiopine started on 5.5.13 3 days prior to death	+		-	Death : Myasthenic crisis, Resp. failure, autonomic dysfunction, Shock : HBsAg +ve status. Admitted in 2011 thrice plasmapharesis 5 cycles done each time for crisis.
23	60	M	pyridostigmine	Methyl Prednisolone	-	-	+	-	-	Death : Pt. stopped drug 1 day prior to admission myasthenic crisis, pneumonia.
24	45	F	pyridostigmine	T. Prednisolone Inj. Methyl Prednisolone	-	Azathioprine	+	-	3 cycles completed	Expired
25	40	M	pyridostigmine	-	-	Azathioprine	+	-	5 cycles given	Improved

MASTER CHART 2

S. NO	AGE	SEX	DISEASE DURATION (Days)	PREDISPOSING FACTOR	INTERVAL FROM SYM TO CRISIS (Days)	DURATION OF CRISIS (Days)	DURATION IMCU STAY (Days)	TREATMENT		TIME FOR DISEASE STABILIZATION		COMPLICATION	THYMOMA	THYMECTOMY	OUTCOME	
								IVIG	PLASMA PHERESIS	NO. OF DAYS FOR EXTUBATION	DRUG RECEIVING				IMPROVEMENT	DEATH
1	43	F	7	SPINE TB, ASPIRATION	7	30	40	+	+	30	P+S	VAP	NEG	OPERATED AFTER STABILIZATION	YES	-
2	38	F	1095	UTI	1095	15	20	-	-	15	P+S+M.PRED	-	NEG		YES	-
3	35	M	90	-	60	10	15	-	+	NASAL 02	P+S+A	-	NEG	OPERATED AFTER 1 MONTH OF MG DIGANOSIS	YES	-
4	48	M	1460	-	1460	30	30	+	+	30	P+S	VAP	NEG	NOT OPERATED	-	EXPIRED
5	27	M	545	VIRAL FEVER	545	5	15		+	5	P+S+A	-	(+)	NOT OPERATED	YES	-
6	19	M	90	ENTERIC FEVER	90	5	10	-	-	5	P+S	-	NEG	-	YES	-
7	31	M	20	-	20	5	7	-	-	5	P+S	-	NEG	-	YES	-
8	63	F	1095	-	730	7	12	-	+	7	P+A	-	NEG	OPERATED	YES	-
9	51	M	7	-	7	2	7	-	-	2	P+S+A	-	(+)	OPERATED	YES	-
10	45	F	180	-	180	5	5	-	-	NASAL 02	P+S	-	NEG	-	YES	-
11	32	M	730	-	730	10	10	-	+	NASAL O2	P+S+A	-	NEG	OPERATED	YES	-
12	34	M	730	-	545	7	12	+	+	7	P+S+A+ MYCO.MOF	-	NEG	OPERATED	YES	-
13	45	M	545	RESP. INFECTION	300	14	20	-	+	14	P+S	-	NEG	-	YES	-
14	17	M	365	RESP. INFECTION	180	5	7	-	+	NASAL O2	P+S	-	(+)	ADVISED OPERATION	YES	-
15	30	F	910	RESP. INFECTION	545	4	8	-	+	NASAL O2	P+S	-	(+)	ADVISED OPERATION	YES	-

S. NO.	AGE	SEX	DISEASE DURATION (Days)	PREDISPOSING FACTOR	INTERVAL FROM SYM TO CRISIS (Days)	DURATION OF CRISIS (Days)	DURATION IMCU STAY (Days)	TREATMENT		TIME FOR DISEASE STABILIZATION		COMPLICATION	THYMOMA	THYMECTOMY	OUTCOME	
								IVIG	PLASMA PHERESIS	NO. OF DAYS FOR EXTUBATION	DRUG RECEIVING				IMPROVEMENT	DEATH
16	58	F	1095	URI	545	5	10	-	+	NASAL O2	P+S	-	NEG	ADVISED OPERATION	YES	-
17	54	M	365	FEVER	365	5	10	-	+	NASAL 0O2	P+S	-	(+)	OPERATED	YES	-
18	39	F	180	-	180	5	5	-	+	5	P+M.Pred	-	NEG	-	YES	-
19	60	M	365	ASPIRATION	150	12	15	-	+	12	P+S	-	NEG	-	YES	-
20	36	F	90	RESP INFECTION : DRUG DEFAULT	90	3	7	-	+	NASAL 02	P+S	-	NEG	-	YES	-
21	65	F	240	FEVER	240	30	40	-	+	30	P+S	VAP	NEG	-	YES	-
22	37	F	1460	HBsAg +VE	365	5	3	-	2011 : Thrice crisis each time PE 5 times	3	P+S+A	RESP FAILURE, AUTONOMIC DYSFUNCTION, SHOCK	NEG	-	-	EXPIRED AFTER 3 DAYS
23	60	M	1460	PNEUNOMIA, LOOSE STOOL, PT. STOPPED DRUG 1 DAY, PRIOR TO ADMISSION	730	5	7	-	-	5	P+M.Pred	-	NEG	-	-	EXPIRED
24	45	F	1460	ASPIRATION	1460	10	8	-	+	10	P+M.Pred+A	RESP. FAILURE, LT. PL. EFFUSION WITH CONSOLIDATION & COLLAPSE OF LT. LOWER LOBE RT. PNEUMOTHORAX SUBCUTANEOUS EMPYSEMA	NEG	-	-	EXPIRED
25	40	M	1095	URI	365	7	10	-	+	7	P+A	-	(+)	NOT OPERATED	YES	-

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
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CERTIFICATE OF APPROVAL

To
Dr.M.Jayakumar,
PG in Neurology,
Madras Medical College,Chennai -3

Dear Dr.M.Jeyakumar,

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled " Myasthenic Crisis – Analysis of predisposing factors, clinical features, associated complications and treatment outcome" No.32112012.

The following members of Ethics Committee were present in the meeting held on 01.11.2012 conducted at Madras Medical College, Chennai -3.

1. Prof. R. Nandhini MD -- Member Secretary
   Director, Instt. of Pharmacology ,MMC, Ch-3
2. Prof. Reghu MD -- Member
   Director , Inst. Of Internal Medicine, MMC, Ch-3
3. Prof. Shyamraj MD -- Member
   Director i/c , Instt. of Biochemistry , MMC, Ch-3
4. Prof. P. Karkuzhali. MD -- Member
   Prof., Instt. of Pathology, MMC, Ch-3
5. Prof. G.Muralidharan MS -- Member
   Prof of Surgery, MMC, Ch-3
6. Thiru. S. Govindsamy. BA,BL -- Lawyer

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

R Nadini 23/11/12
Member Secretary, Ethics Committee