Study on mods - “an emergent disease of medical progress”

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Abstract

Multiple organ dysfunction syndrome (MODS) is a systemic, dysfunctional inflammatory response that requires longer admissions in acute medical care unit with high mortality rate. The present study was done prospectively to evaluate clinical profile and etiological spectrum of patients admitted in acute medical care unit categorized under multi-organ dysfunction syndrome (MODS) and to correlate outcome of MODS. 50 patients of ≥18 years age who were admitted in Acute Medical Care Unit, Department of Medicine, Government General Hospital, Kakinada, with more than one organ dysfunction, requiring intervention were studied during 2010-2012. In all cases provisional diagnosis was made by taking detailed history and clinical examination, and were subjected to the relevant investigations. The criteria were used to include under MODS were assessed on respiratory, renal, gastrointestinal, central nervous system, Glasgow coma scale cardiovascular, hematological parameters. The outcome of MODS was correlated by application of APACHE-II score on admission day, serial SOFA score on day 1 and 3, serial serum albumin measurement on day 1 and 5. There was multiorgan involvement. Most common organ failed was renal 30 (60%), followed by CNS 27 (54%), respiratory 25 (50%), CVS 23 (46%), GIT 17 (34%), Hematologic 9 (18%). Sepsis was the most common cause of MODS in 24 (48%) patients. Most common organ dysfunction as a predictor of mortality was CNS in 17 (77%) out of 22 patients expired, followed by Respiratory in 13 (59%), Renal 11 (50%), CVS 10 (45%), GIT 9 (40%), Hematologic 2 (9%). Maximum incidence of mortality was seen when ≥5 organs failed. There was significant correlation statistically in our study between APACHE II score on admission and outcome as Pearson chi-square “p”< 0.001Mean SOFA score of survivors on day 1 was 6±2 and on day 3 was 2±1. Mortality significantly decreased (3.44%) on day 3 if SOFA score was ≤7. Multi-Organ Dysfunction Syndrome (MODS) was common in younger age group with the mean age of40 years. Sepsis (48%) was the most common cause of MODS, followed by other causes. Maximum incidence of mortality (55%) was seen if the first failed organ was respiratory system and when ≥5 organs failed. Highest incidence of mortality was seen in 8th decade (100%). APACHE II score on admission, serial SOFA scores, and serial albumin measurements can help ICU physicians in admitting patients, monitoring the clinical course, assessment of organ dysfunction, predicting mortality and for transferring patients out from ICU and thus in proper utilization of ICU resources.

Key words: Multiorgan Dysfunction; Failure; Intensive Care Unit

INTRODUCTION

Multiple Organ Dysfunction Syndrome (MODS)’, term was unheard till the early 1970s. This probably reflects the fact that patients could not be kept alive long enough for the sequential dysfunction of organs to develop.¹ MODS is an important cause of morbidity and mortality in intensive care units world over.²³ The term “multiple organ dysfunction syndrome” (MODS) was proposed in 1991 by a Consensus Conference of the American College of Chest physicians (ACCP) and the society of Critical Care Medicine.⁴ A more recent definition of MODS was provided by John Marshall as “the development of potentially reversible physiologic derangement involving two or more organ systems not involved in the disorder that resulted in ICU admission, and arising in the wake of a potentially life threatening condition.”

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physiologic insult.\textsuperscript{5} The multiple organ dysfunction syndrome arose paradoxically as the result of advances in supportive therapy, and in this sense MODS can be viewed as a “disease of medical progress”. Even today, MODS remains as the leading cause of death in intensive care units.

The septic process is usually triggered when microorganisms spread from GIT or skin into the contiguous tissues or may be introduced directly into the blood stream. Direct injury or insult to an organ system results in primary MODS and indirect injury to one or more organ systems, a consequence of host response which results in an immuno-inflammatory response in organs distant from site of initial insult leads to secondary MODS.

The key pathogenetic mechanisms underlying the evolution of MODS\textsuperscript{1,6,7} are local responses which initiates systemic response, which may progress to massive systemic inflammation, excessive immunosuppression, final stage of MODS Immunologic dissonance (Figure-1,2,3). Death will ensue from organ failure or infection unless the immune system can recover.

**MATERIALS AND METHODS**

Study was carried out in 50 patients of \( \geq 18 \) years age who were admitted in Acute Medical Care Unit, Department of Medicine, Government General Hospital, Kakinada, with more than one organ dysfunction, requiring intervention for maintaining homeostasis, during 2010-2012. In all cases provisional diagnosis was made by taking detailed history and clinical examination, patients who fulfilled the inclusion criteria were taken into the study and were subjected to the investigations which included Complete blood picture (Hb, TLC, DC, ESR) Complete urine examination (protein, sugar, microscopy, ketones) Random Blood Sugar, Renal function tests (blood urea, serum creatinine) Liver function tests (total bilirubin, direct bilirubin, ALT, AST, ALP, albumin),Chest

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**Figure-1. Overview of cellular and molecular mechanisms leading to MODS. TLR, Toll like receptor; ACS, abdominal compartment syndrome**
X-ray, ECG, Arterial blood gases, Serum sodium and potassium, blood cultures and Platelet count. Peripheral smear, OBC for malarial parasite, ultrasound abdomen, CT imaging, urine and other body fluid cultures were also done when indicated. The following criteria used to diagnose MODS was taken systemically as follows:

- Respiratory: Arterial hypoxemia – PaO\(_2\)/FiO\(_2\) < 300.
- Renal: Rise in Creatinine by > 0.5 mg/dl from baseline or urine output <0.5 ml/kg/hr for at least 2 hours.
- Gastrointestinal: Ileus or plasma total bilirubin > 4 mg/dl.
- Central nervous system: Glasgow coma scale < 6.
- Cardiovascular: SBP < 90 mm Hg or MAP < 70 or SBP decrease > 40 mm Hg.
- Hematological: Platelet count < 100,000/\(\mu\)l or INR > 1.5 or a PTT > 60 seconds.

Figure 2. Crosstalk between the intestinal epithelium, immune system and commensal bacteria is a central to initiating systemic inflammatory response\(^4\).

Patients categorized under MODS due to burns, trauma and post-operatively were excluded from the study. The outcome of MODS was correlated by application of APACHE-II score on admission day, serial SOFA score on day 1 and 3, serial serum albumin measurement on day 1 and 5

### RESULTS

The entire cohort consisted of 50 patients, of which majority of patients were in the age group of 21-30 years (30%), the range being 18-75 years. Mean age of presentation is 40±17.2. (Table 1) 27 (54%) were males and 23 (46%) were females. Most common presenting symptoms were fever in 37 (74%) patients and shortness of breath in 36 (72%). The other symptoms include oliguria23 (46%), jaundice 19 (38%), cough 14 (28%), and altered sensorium 10 (20%), bleeding manifestations 5 (10%) (Table 2).

### Table-1. Age distribution

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Age Distribution</th>
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<tr>
<td></td>
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<tr>
<td>18-20</td>
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<tr>
<td>21-30</td>
<td>15</td>
</tr>
<tr>
<td>31-40</td>
<td>8</td>
</tr>
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<td>61-70</td>
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</tr>
<tr>
<td>71-80</td>
<td>3</td>
</tr>
</tbody>
</table>

Amongst the manifestations of SIRS, tachypnea was the most common in 46 (92%) patients, followed by tachycardia 44 (88%), temperature 43 (86%), leukocytosis 29 (58%). Out of 50 patients, serum creatinine was found to be elevated by >0.5 mg/dl from baseline in 30 (60%) and blood urea > 40 mg/dl in 37 (74%) (Graph 1).

### Table-2. Clinical symptomatology

<table>
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<th>Symptom</th>
<th>Clinical Symptomatology</th>
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<td></td>
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<td>Fever</td>
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<tr>
<td>Shortness of breath</td>
<td>36</td>
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<tr>
<td>Decreased urine output</td>
<td>23</td>
</tr>
<tr>
<td>Jaundice</td>
<td>19</td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
</tr>
<tr>
<td>Altered sensorium</td>
<td>10</td>
</tr>
<tr>
<td>Bleeding manifestations</td>
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</table>

### Table-3. Processing Summary

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<th>Missing</th>
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</thead>
<tbody>
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<td>%</td>
<td>No.</td>
</tr>
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<td>Age * outcome</td>
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</tr>
<tr>
<td>1st organ failed * outcome</td>
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<tr>
<td>No. of organs * outcome</td>
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<td>Albumin d1 * outcome</td>
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</tr>
<tr>
<td>Albumin d5 * outcome</td>
<td>50</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
Most common electrolyte abnormality was hyperkalemia in 21 (42%) patients, followed by hyponatremia 20 (40%), hypokalemia 10 (20%), hypernatremia 1 (2%). The most common hepatic dysfunction was elevation of transaminases (ALT>60, AST>40) seen in 33 patients (66%), high alkaline phosphatase (>150 KA) in 6 (12%), bilirubin > 4mg/dl in 17 (34%), INR >1.5 in 6 (12%).

Out of 50 patients, tachycardia was seen in 44 (88%), hypotension in 23 (46%) and 23 (46%) patients needed inotropic support. Out of 50 patients, thrombocytopenia < 100,000/μl was found in 6 (12%), the lowest platelet count being 46,000/μl, INR >1.5 in 6 (12%), bleeding manifestations were seen in the form of ecchymosis and purpurae in 5 (10%). Out of 50 patients, Glasgow coma scale < 6 was seen in 27 (54%)., ARDS was found in 14 (28%) and Acute Lung Injury in 11 (22%). Among the 25 patients with respiratory involvement, mechanical ventilator support was required in 15 patients (60%).

There was multiorgan involvement. Most common organ failed was renal 30 (60%), followed by CNS 27 (54%), respiratory 25 (50%), CVS 23 (46%), GIT 17 (34%), hematologic 9 (18%) (Table-3). Sepsis was the most common cause of MODS in 24 (48%) patients, followed by complicated malaria in 12 (24%), disseminated Koch’s in 3 (6%), Parquet poisoning in 2 (4%), drug induced (anti-TB drugs) in 2 (4%), other causes in 7 (14%) patients were. H1N1 influenza, pancreatitis, dengue, chronic kidney disease, stroke, pneumo-cystisarcani pneumonia, chronic rheumatic heart disease (Graph-2). Most common organ involved in sepsis was cardiovascular (70.8%), whereas in patients diagnosed with malaria, it was renal (58.3%). Bacterial infections were found in 13 (26%) patients, malaria in 12 (24%), fungal infection in 1 (2%). Out of 24 patients with Sepsis, bacterial infections were found in 13 (26%), of which Gram negative organisms were seen in 9 (18%) whereas Gram positive in 5 (10%), Sterile in 10 (20%). Amongst the 9 Gram negative infections, E.coli was isolated in 3 (33.3%), Klebsiella and Pseudomonas in 2 (22.2%) each, Acinetobacter in 1 (11.1%) and polymicrobial – E.coli + Klebsiella in 1 (11.1%). Amongst the 4 gram positive infections, Staphylococcus aureus was isolated in 3 (75%) and Streptococcus in 1 (25%). Most common site of infection was respiratory...
tract in 13 (26%) patients, skin and soft tissue infections 8 (16%), urinary tract 3 (6%), GIT 2 (4%), CVS 2 (4%), CNS 2 (4%) (Graph-3).

Graph 1. Manifestations of SIRS

Graph 2. Multiple Organ Involvement

Out of 50 patients who were taken for this study, 22 (44%) patients expired during their hospital stay. The age group specific mortality rate shows a rise in mortality as age increases, with least incidence of 16.7% in 18-20 age group and highest incidence of 100% in 71-80 age group. (TABLE4). Most common organ dysfunction as a predictor of mortality was CNS in 17 (77%) out of 22 patients expired, followed by Respiratory in 13 (59%), Renal 11 (50%), CVS 10 (45%), GIT 9 (40%), Hematologic 2 (9%). Maximum incidence of mortality was seen when ≥5 organs failed (100%), 4 organs (75%), 3 organs (80%), 2 organs (14%).

Statistical analysis was done among 8 variables to correlate with outcome by using IBM SPSS 17.0 software. The 8 variables were age, first organ failed, total number of failed organs, APACHE II on admission day, SOFA score on day 1 and 3, and serum albumin on day 1and 5. Valid Process summary of analysis in total 50 patients .There was no significant correlation statistically in our study between age and outcome and between first failed organ and outcome as pearson chi-square “p”= 0.163. There was significant correlation statistically in our study between total number of failed organs and outcome as pearson chi-square “p”=0.014. The following are the chi-square tests used in this analysis. Mean APACHE II score of survivors was17±6 and of non-survivors 33±11. There was significant correlation statistically in our study between APACHE II score on admission and outcome as pearson chi-square “p”< 0.001. The following are the chi-square tests used in this analysis (Graph-4).

Graph 3. Causes of Multiple Organ Involvement

Mean SOFA score of survivors on day 1 was 6±2 and on day 3 was 2±1. Mean SOFA score of non-survivors on day 1 was 9±4 and on day 3 was 17±6. On day 1 if SOFA score was ≥15 and on day 3 if ≥ 8, incidence of mortality is 100 %. Mortality significantly decreased (3.44%) on day 3 if SOFA score was ≤7. There was significant correlation statistically in our study between SOFA score on day 1 and outcome as pearson chi-square “p”< 0.001. The following are its chi-square values: (Table 5).

Graph 4. APACHE Score Vs Mortality

DISCUSSION

In our study, cohort consisted of 50 patients of which 27 (54%) were male and 23 (46%) were female, with
male to female ratio being 1.17:1. Age range was 18-75 years with majority (30%) being in 21-30 years.

**Graph-5 Sofa Score Vs Outcome**

Incidence of MODS in females in our study was higher when compared with those of study done by Elizabeth Bilevicius et al. from UNICAMP teaching hospital, Brazil where in out of 54 patients 37 (69%) were male and 17 (31%) female, age range being 15-80 years. In our study the percentage incidence of the following clinical features were comparable with those of UIHC study done by Trish.M.Perl et al from Iowa hospitals except for the incidence of mental status changes and hypotension, the incidence in our study being 20% and 46% respectively compared to 42% and 61% in UIHC study.

In our study, we observed a great number of patients who had renal failure 30/50 (60%) which is comparable to El. Bilevicius et al. study where it was 27/54 (54%). This trend was not seen in other studies. The incidence of renal failure in both Rangel Frausto et al. and UIHC study was 19%. This may be due to high incidence of renal failure (58%) with complicated malaria in our study.

In our study, the incidence of GIT dysfunction was 34% (17/50) comparable to El. Bilevicius et al. study where in it was 33% (18/54) and higher compared to UIHC study, where in it was 25%.

In our study, the most common CNS manifestation was encephalopathy found in 54% (27/50) which was very high compared to 25% in UIHC study. This may be due to high incidence of cerebral malaria (24%) in our study and late presentation of patient to the hospital.

In our study, incidence of respiratory failure in form of ALI and ARDS was 50% (25/50) which was very low compared to El. Bilevicius et al. study where in it was 94%. This may be due to inclusion of post-operative patients in their study. Bone RC et al. reports its incidence of respiratory failure as 25%.

In our study, the incidence of CVS dysfunction was 46% (23/50) which was very low when compared to El. Bilevicius et al. study, as they have also included burns, peritonitis and post-operative patients with MODS.

In our study, the incidence of hematological dysfunction in the form of thrombocytopenia and DIC was 18% (9/50) which is comparable to El. Bilevicius et al. study where in it was 22%. In our study, the incidence of complicated malaria is 24% (12/50), out of which Plasmodium vivax was 16% (8/50) and Plasmodium falciparum 8% (4/50). Incidence of sepsis was 48% (24/50). There were no studies in literature comparing both sepsis and non-sepsis causes of MODS.

In our study, out of 24 patients with sepsis, blood culture was positive in 14 (58.3%), which is higher when compared to El. Bilevicius et al. study where in it was 42% (23/54). This difference may be probably due to inclusion of immunocompromised patients with HIV, chronic kidney disease on hemodialysis, chronic steroid usage etc. in our study. In our study we did not isolate Enterobacter, Staphylococcus epidermidis, and MRSA, that were isolated in El. Bilevicius et al. study. We have identified one patient with H1N1 influenza by means of throat swab presenting with MODS.

In our study, overall mortality in MODS was 44% (22/50), which was slightly lower when compared to 55% (30/54) in El. Bilevicius et al. study, as we have included both septic and non-septic causes of MODS.In our study, there was 100% mortality in ≥71years age group which is comparable to >95% mortality in studies done by Zimmerman et al., Hebert P.C. et al., Gullo et al. In our study, maximum incidence of first failed organ as respiratory system was 38%. In our study, there was a strong statistical correlation (p=0.014) between total number of organs and mortality rate which is comparable to Hebert et al. who also found a strong linear correlation. This is also comparable to Gullo and Berlot study who described that the most common first organ failed was lung.

The incidence of mortality in our study with 2 failed organs was 14%, 3 organs-80%, 4 organs-75%, ≥5 organs-100%. This is comparable to other studies that showed diversity of results with mortality rates varying from 20-76% with 2 organs failure, 30-90% with 3 organs. Majority of studies showed mortality of 100% with ≥4 organ failure. Hebert et al. found mortality of 100% in ≥5 organs failure which is comparable to 100% mortality in ≥5 organs in our study. Though the number of samples in both studies were small and did not permit generalization, the same trend was observed in whole literature with larger samples.
Mean APACHE II score of survivors in our study was 17±6 and of non-survivors was 33±11, which was less than that of El. Bilevicius et al. study, where mean score of survivors was 21±18 and non-survivors was 42±26. Our study had lower standard deviation of error when compared to El. Bilevicius et al. study in both groups.

In our study there was a strong statistical correlation between APACHE II score and mortality p<0.001, comparable to that of El. Bilevicius et al. study, where p<0.002.

Comparing our study with Knaus et al study in relation to APACHE II scoring and mortality, our study had similar values of mortality if score is ≥25. This difference was probably due to less sample size (n=50) compared to Knaus et al (n=5815).

We have compared SOFA score on day 1 and 3 with outcome, as previous studies carried out by Acharya SP et al. Vincent JL et al. Ferreira et al. have compared serial SOFA scores with 48 hour interval.

In our study, when SOFA score was compared to outcome, non-survivors had high day 1 (9±4) and day 3 (17±6) as compared to survivors on day 1 (6±2) and day 3 (2±1). We also found significant statistical correlation between day 1, 3 SOFA score and outcome with p value <0.001 comparable to study done by Acharya SP et al, where in p value <0.02.

Initial (day 1) SOFA range in our study was 2-17 similar to 1-17 in Acharya SP et al. study. Initial SOFA >11 was associated with 100% mortality in our study which was similar to >90% mortality in Vincent JL et al studies Acharya SP et al. Mortality significantly decreased in our study on day 3 if SOFA ≤7 to 3%, which was comparable to 8% in the study done by Ferreira et al.

However, further studies with greater number of patients, more frequent measurements of variables and comparison between different scoring systems is required to improve the accuracy.

**CONCLUSIONS**

Multi-Organ Dysfunction Syndrome (MODS) was common in younger age group with the mean age of 40 years and in males. Most common cause of MODS was sepsis. Maximum incidence of mortality was seen when ≥5 organs failed. APACHE II score on admission, serial SOFA scores, and serial albumin measurements can help ICU physicians in assessment of organ dysfunction, predicting mortality and thus in proper utilization of ICU resources. In current ICU practice, treatment is focused on prevention and treating individual organ dysfunction as it develops. With increased understanding of the pathophysiology of MODS therapy will come newer modalities which inhibit or interfere with the propagation of the endogenous systemic inflammatory response.

**Competing interests**

Authors declares that they have no Conflict of Interest. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Institutional and National) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all the patients for all diagnostic and therapeutic procedures. It does not contain any studies with animal subjects.

**REFERENCES**