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# Comparison Of Demographic ,Clinical ,Radiological Characteristics & Comorbidies In Survived & Nonsurvived Adult Patients Admitted In ICU With Confirmed Diagnosis Of Influenza A (H1N1)

Medical Science

**KEYWORDS :** XRC- X ray chest , RN- Reticulonodular ,DM –Diabetes Mellitus , HT – Hypertension NS –Not significant , RVHD

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## ABSTRACT

*Introduction :- Seasonal influenza is an acute respiratory illness that occurs particularly during the winter months .Type A virus is the most virulent & this virus can mutate easily . The novel H1N1 virus has the features of North American and Eurasian swine, avian & human influenza*

*Objectives :- To correlate demographic,comorbidities,clinical &radiological characteristics in survived &nonsurvived adult patients with confirmed diagnosis of InfluenzaA (H1N1).*

*Material & methods:-Retrospective study of 100 RT-PCR confirmed patients from August 2009 to March 2010 was done.*

*Results:-Equa l(14) number of males & females died. Mean age of nonsurvivors was 34.43 yrs. Mortality was more with pregnancy (n=5),HT(n=4),DM(n=3)&RVHD (n=3).Major clinical findings in nonsurvivors were fever 26(92.85%) ,cough 27 (96.42%) , breathlessness ,22 (78.57%) ,throat-pain10(35.71%),bodyache 03(10.71%),rhinorrhoea08 (28.57%), tachypnoea 14(50.00%) &crepitations17 (60.71%). Mean duration of stay was7.7days for nonsurvivors.20(71.42%)with RUZ,10(35.71%) with LUZ,25(89.28%) with RMZ,24 (85.71%) with LMZ, 26(92.85%) with RLZ, 21(75%)withLLZ involvement died.RUZ RMZ ,LMZ (P<0.001),RLZ(P<0.01)involvement was statistically significant for mortality. 43(59.72%) with consolidation ,16(22.22%) with reticulonodular & 06(08.33%)with nodular pattern survived.06 (20.00%) with single zone ,09(32.00%) with two,09(32.00%) with three, 10(33.33%) with four, 04(14.29%) with five & 10(36.37%) with six zone involvement died. Age (likelihoodratio-0.67),Gender (Fischer Exact test 0.824),comorbidity and symptoms (except tachypnoea(p<0.01),mean duration of stay,radiological pattern, number of zones were not statistically significant. RLZ, RMZandLMZ affection indicated high mortality , and no involvement indicated increased probability of survival .Out of 35 patients requiring ventilator 28 died .*

*Conclusions: Mortality was more in Young to middle age patients ,in presence of Pregnancy, HT,RVHD,COPD, patients requiring ventilation, when RMZ,LMZ and RLZ,LLZ affected, no involvement of these zones indicated increased probability of survival upto 90-92% ) . LUZ involvement signified higher recovery rate.*

**Introduction :-**

In June 11, 2009, the World health Organization declared the H1N1 Influenza infection as a global pandemic after at least 3 months of the confirmed diagnosis of the first case in California[1]. India reported its first case of Novel 2009 influenza A (H 1N1) virus in May 2009 & subsequently, it was diagnosed all over the country within a short period of time. First case in Pune (Maharashtra) was reported in August 2009 & since then Novel 2009 influenza A (H1N1) infection had significantly affected the population. Many patients during 2009 pandemic required Mechanical ventilation for management . It was the first pandemic with such a demand for critical care services . In Pune, during the pandemic, a significant number of patients became critically ill primarily because of respiratory failure . Many patients needed ICU management , intubation & mechanical ventilation (unpublished data). The description & correlation of demographic characters ,comorbidities , clinical & radiological characteristics in survived & death patients in India's population has not been published yet. We therefore conducted a retrospective review of medical records of survived & died adult patients admitted with confirmed diagnosis of Novel 2009 influenza A (H1N1) virus infection in critical condition in ICU .

**Material & Methods:-**

**Study Period and Population:** Available hospital records were retrospectively reviewed for adults with PCR-confirmed 2009 H1N1 infection, and admitted to Intensive care unit of Sassoon General Hospital (SGH)-Byramjee Jeejeebhoy Medical College (BJMC),Pune between August 2009 and April 2010. This is single center retrospective study . Patients were admitted in Intensive care unit because either they had ARDS requiring mechanical ventilator or tachypnoea >24 breaths per minute or hemoptysis or hypotension requiring vasopressor support. All these patients were treated with antiviral drugs ie cap Oseltamivir 150 mg twice a day orally or through Ryles tube and Zanamavir inhalation 10 mg twice a day ,Vasopressor support whenever required ,Antibiotics & Supportive treatment , conventional invasive & noninvasive mechanical ventilation.

Out of 103 patients admitted in the ICU during August 2009 to April 1010 , we could not get proper records of three patients so clinical , comorbid & radiological findings were evaluated in one hundred patients .

**Data Collection**: Clinical data were extracted from available hospital records. The following information was collected: demographic characteristics on admission including age, gender ; clinical characteristics on admission including duration of symptoms, co-morbid illnesses (like Pregnancy, Obesity , Diabetes Mellitus , Hypertension ,Immunocompromised State like HIV , RVHD , COPD) ; clinical findings at presentation and radiologic abnormalities. Intubation & whether on mechanical ventilator or not was also recorded.

**Diagnosis of 2009 H1N1 Influenza:** Influenza-like illness was de-

fined by the documentation of fever (temperature ≥ 100°F), and/or cough, and /or headache or sore throat, with any of the following symptoms: myalgia or arthralgia , respiratory distress, or vomiting or diarrhea, chest pain , abdominal pain .

All adults admitted with influenza-like illness, underwent nasopharyngeal (NP) aspirate or swab specimen collection for Influenza A (H1N1) detection on the day of hospitalization. Patient specimens were sent to the National Institute of Virology (NIV) in Pune, a world health organization (WHO) designated influenza center, where Real time reverse-transcriptase PCR assay was performed according to the protocol recommended by the U.S. Centers for Disease Control and Prevention (CDC)[2] and results communicated within 24 hours. For the purposes of this analysis, an adult was defined as infected with 2009 H1N1 influenza based on laboratory confirmation of the presence of H1N1 specific viral nucleic acid in nasopharyngeal specimen collected on hospitalization.

**Radiology:** All 100 patients underwent chest radiography within 24 hours of admission . All radiography was performed in portal machine of Adonis of 100MA capacity. The chest radiographs were reviewed by two experienced radiologists who were blinded to each other's reports who showed excellent (95%) agreement. Zonal involvement was assessed by drawing an horizontal lines traversing the lung fields from the apex to the domes of the diaphragm at 1/3rd and 2/3 rd distances.

**Data Analysis:** All analyses were carried out utilizing SPSS version 16. Odds ratio , Likelihood ratios , Anova predictive values & F tests were carried out with confidence intervals.

**Ethical Review and Approval:** Due to retrospective nature of the study, with no interventions deviating from standard clinical practice and without the possibility of identification of individual patients from the anonymised collected data , the Ethics Committee of SGH gave ethical approval for the study and waived the need for informed consent of the patients

**Results :-**

As shown in table 1, Our study included total 100 patients, out of which 72 survived while 28 ) died . Equal ( 14 each, Graph 1) number of males & females died. 39 males while 33 females survived . Though more number of males survived, Gender distribution had no bearing on mortality (Fischer Exact test 0.824, Odds ratio 1.182,CI 0.49 –2.83).

Mean age(Graph 2) of the patients who died was 34.43 years while for survived patients it was 33.04 years. however it was not statistically significant (likelihood ratio - 0.67 ) for survival or death .As shown in Graph 3 , 60.71% of patients between 21-30 years of age died .

As shown in Graph 4 & table 1 , 08( % ) patients with pregnancy , 09 (%) with DM, 07( %) with HT , 08 ( %) with obesity , 03 with RVHD (%) , 1 with COPD (%) ,2 with HIV (%) survived while 05( % ) patients with pregnancy , 03(%) with DM, 04( %) with HT , 02 ( %) with obesity , 03 with RVHD (%) , 2 with COPD (%) ,1 with HIV (%) & 1(%) with CVA died. Though more number of deaths were in pts with Pregnancy (n=5 , 17.85%), HT (n=4 , 14.28%), DM (n= 3, 10.71%) & with RVHD(n= 3 ,10.71%), none of the comorbidity had statistically significant relation with mortality or survival.

Mean duration of hospital stay was 6.7 days for survived patients & 7.7 days for died patients & is not statistically significant.

As shown in table 2 , Amongst survivals ,fever was present in 70(97.22%),cough in 68(94.44%), breathlessness in 64(88.88%) , throat pain in 23(31.94%) , bodyache in 14(19.44%), rhinorrhoea in 18(25.00%) , tachypnoea in 53(73.61%) & crepitations in 59(81.94%) while amongst death patients fever was present in 26(92.85%) ,cough in27(96.42%) ,breathlessness in22 (78.57%),throat pain in10(35.71%), bodyache in03(10.71%), rhinorrhoea in 08(28.57%), tachypnoea in14(50.00%) & crepitations were present in17(60.71%). However except Tachypnoea (p<0.01 (CI 95% CI= 1.13 – 6.90) no other symptom was statistically significant for mortality or survival outcome.

As shown in table 3 & Graph 5, 28(38.88%) patients with right upper zone involvement survived while 20(71.42%) patients with RUZ involvement died & is statistically significant for mortality outcome (P<0.001). 20( 27.77%) patients with Left upper zone involvement survived while 10(35.71%) patients with LUZ involvement died & is statistically not significant for mortality or survival outcome . 43(59.72%) patients with right middle zone involvement survived while 25(89.28%) patients with RMZ involvement died & is statistically significant for mortality outcome (P<0.001). 02(02.77%) patients with left middle zone involvement survived while 24(85.71%) patients with LMZ involvement died & is statistically significant for mortality outcome (P<0.001). 49(68.05%) patients with right lower zone involvement survived while 26(92.85%) patients with RLZ involvement died & is statistically significant for mortality outcome (P<0.01). 45(62.50%) patients with left lower zone involvement survived while 21(75%) patients with LLZ involvement died & is statistically not significant for mortality or survival outcome.

As shown in Graph 6 , 43(59.72%) patients with consolidation survived while 16(57.14%) patients with consolidation died. 16(22.22%) patients with reticulonodular pattern survived while 06(21.42%) patients with reticulonodular pattern died . 06(08.33%) patients with nodular pattern survived while 04(14.28%) patients with nodular pattern died .None of the radiological pattern is statistically significant for survival or death outcome.

As shown in Graph 7 , All patients with no zone involvement survived. 58 (80.00%) patients with single zone involvement ,49 (68.00%) with two zone ,48(66.66%) with three zone , 47(65.00%) with four zone ,62(85.71%) with five zone & 46(63.63%) with six zone involvement survived while 06(20.00%) with single zone ,09(32.00%) with two zone,09(32.00%) with three zone , 10(33.33%) with four zone, 04(14.29%) with five zone & 10(36.37%) with six zone involvement died . The number of zones of lung involvement shown in X-ray had no bearing on the survival or death

As shown in table 4 ,based on zonal involvement, RLZ, RMZ and LMZ affection indicated high mortality (high sensitivity), and no involvement of these zones indicated high negative predictive value (increased probability of survival upto 90-92%)

Out of 35 patients requiring mechanical ventilator 28 died .All 28 who died required invasive mechanical ventilator for case management while four patients who requied noninvasive mechanical ventilator survived .

**Discussion:**

Seasonal influenza is an acute respiratory illness that occurs particularly during the winter months . Type A virus is the most virulent & this virus can mutate easily[3] The novel H1N1 virus has the features of North American and Eurasian swine, avian & human influenza[1] A lot has been mentioned in the literature on the mortality outcome & mortality predictors in patients diagnosed with H1N1 Influenza .Mortality in hospitalized H1N1 patients has varied from 7% to 11% (Jain et al. 2009)[4]; (Louie et al. 2009)[5], in ICU patients from 13% to 41%, patients on MV from 46% to 58% , and patients treated with ECMO from 14% to 56% (Davies et al. 2009)[6]; (Chan et al. 2010)[7]; (Freed et al. 2010)[8]; (Grasselli et al. 2011)[9]; (Patroniti et al. 2011)[10]; (Roch et al. 2010)[11].

The most common direct cause of death was respiratory failure (76%) according to an English study (Donaldson et al. 2009)[12]. Diffuse alveolar damage is characteristic in autopsy (Bai et al. 2011)[13]; (Mauad et al. 2010)[14]; (Perez-Padilla et al. 2009)[1]. Hyaline membranes, necrotizing bronchiolitis, and fibroblast proliferation are also found (Bai et al. 2011)[13]; (Mauad et al. 2010)[14].

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A high SOFA score in H1N1 patients was not associated with as high mortality as in other ICU patients (Shahpori et al. 2011)[15]. Multi-organ failure was the cause of death for 18% of patients in England (Donaldson et al. 2009)[12]. In the ECMO group in Italy, 57% died of MODS, and 21% of septic shock (Patroniti et al. 2011)[10]. More than two thirds of the non-survivors had at least one underlying medical condition (Donaldson et al. 2009)[12]; (Louie et al. 2009)[5]. In contrast, 59% were previously healthy according to a report from United Kingdom (Nguyen-Van-Tam et al. 2010)[16]. Obesity was related to more severe disease (Fuhrman et al. 2011)[17], but not to death (Brun-Buisson et al. 2011)[18].

Our case series of ICU hospitalized, seriously ill patients with 2009 H1N1 influenza infection during the H1N1 India pandemic depicts the survivcal & mortality in terms of age , gender , comorbidities , clinical features & radiological findings .

Patients in our cohort were adults younger ( age between 21-40 yrs) than expected for seasonal influenza . We observed more deaths in Young to middle age patients . Maximum number of deaths were bet 21 to 40 years of age (82.14% , n=23) followed by deaths (10.71% , n=03) between 41 to 60 years of age while only 02(07.14% ) patient above the age of 60 died . When age was analysed statistically , it was found to be statistically significant for mortality outcome ( p<0.003). This we attribute to exposure of young to middle age patients first time without having any cross reacting anti bodies against influenza illness while only two deaths in patients with age more than 60 years due to existence of a high frequency of cross-reacting antibodies protecting the elderly .Though more number of males survived [54.16 **(%) vs** 45.83 **(%)]** & equal number of males ( n=14) & females (n=14) died we did not find any statistically significant age difference between survival & death .

Significant number of patients ( n= 63 ) had some form of co-morbidities in our study . The presence of a co-morbid illness like pregnancy , HT ,RVHD & COPD showed a trend towards increased mortality in our series. Though number of deaths were more (n=21,62.62%) amongst pts who had associated comorbidities , when analysed for the bivariate analysis, the co-existing morbidity did not signify any higher or lower risk of death or recovery. However the number of cases are small to draw any conclusions This is in contrast to the observation by different investigators. Severe & complicated clinical course of H1N1 infection has been shown by different investigators among high risk groups[19,20] .Both Survived & death patients had fever , cough, breathlessness ,tachypnea , crepitations as common clinical features however except tachypnea(p <0.01) none of the clinical finding was statistically significant for mortality or survival outcome .

Maximum number of deaths were with consolidation (57.14 %), followed by reticulonodular pattern (21.42%), followed by noular pattern (14.28 %) ,however none of the specific radiological pattern in our study showed statistically significant difference for mortality or survival outcome Though in our study mortality was more with 6 zone involvement , followed by 4 zone involvement , the number of zones of lung involvement has no statistically significant bearing on the survival & mortality .This is in contrast to study by other investigators . Study carried out by Chau TN, Lee PO, Coi KW, et al[21] showed that bilateral disease and involvement of more than two zones were associated with poor clinical outcome. Galit Aviral et al in their study showed more deaths in pts with involvement of four or more lung zones . However sample size in this study was small in this study (total 39, on venti 5, no venti in 34, four or more zone involvement in 5) . Our study showed unique observation . We observed more deaths with RUZ (p<0.001), RMZ (p<0.001),RLZ(p<0.01) & LMZ(p<0.001) involvement & these zone involvement is also statistically significant for mortality outcome . As shown in table 4 ,When specific zonal involvement was analysed for predictivity RLZ , RMZ , LMZ involvement showed high sensitivity (93,89 & 86.75% respectively ) while no involvement of these zones indicated high negative predictive value (92,90%) ie increased probability of survival upto 90-92% . RUZ involvement also has high negative predictive validity upto 85% ie high probability of survival & LUZ involvement signified higher recovery rate .Based on zonal involvement, RLZ, RMZ and LMZ affection indicated high mortality (high sensitivity), and no involvement of these zones indicated high negative predictive value (increased probability of survival upto 90-92%). Only 15.4 % pts showed normal X ray at the time of discharge suggesting that clinical recovery preceds radiological recovery. Reticulonodular pattern was the pattern to disappear most at the time of discharge.

Our study has certain **limitations.** First, its single center retrospective study and the sample size is relatively small. Second we could not correlate other variables like APACHE II score,Pao2/FiO2 ratio, ventilator variables Third we could not compare various types of mechanical ventilation like invasive vs noninvasive for survival or mortality in these patients .. In spite of these limitations, the study is the largest study from India that compared age , gender , comordities , clinical features & radiological characteristics in survivals & death seriously ill influenza A (H1N1) patients needing ICU admission.

**Conclusions:**

Young to middle aged patients had more mortality .Gender distribution had no bearing on mortality. More number of deaths were in presence of Pregnancy , HT ,RVHD,COPD however none of the comorbidy had significant relation with mortality. More deaths were with 6 zone involvement however the number of zones of lung involvement shown in X-ray had no bearing on the survival or death. Based on zonal involvement RMZ, LMZ and RLZ, LMZ if affected showed a high mortality..LUZ involvement signified higher recovery rate., RLZ, RMZ and LMZ affection indicated high mortality (high sensitivity), and no involvement of these zones indicated high negative predictive value (increased probability of survival upto 90-92%) . Mortality was more in Patients requiring invasive ventilation

**Table 1 :-- Correlation of demographic features, comorbidities for mortality outcome**

| Demographic & comorbid Parameter | Survived n=72 (%) | Nonsurvived n=28(%) | Mantle-Haensel odds ratio | Likelihood ratio | Fishers exact test |
|---|---|---|---|---|---|
| Gender | | | | | |
| Male | 54.16 **(%)** | 50.00 **(%)** | 1.182(0.49-2.83) | | 0.824 |
| female | 45.83 **(%)** | 50.00 **(%)** | | | |
| Mean age (yrs) | 33.04 | 33.43 | | | |
| Comorbidities | | | | | |
| Pregnancy | 08.00(11.11) | 05.00 (17.85) | 1.73(0.51-5.86) | 0.769 | 0.50 |
| Diabetes | 09.00(12.5) | 03.00(10.71) | 0.827(0.20-3.30) | 0.074 | 1.00 |
| Hypertension | 07.00(09.72) | 04.00(14.28) | 1.54(0.41-5.76) | 0.410 | 0.72 |
| Obesity | 08.00(11.11) | 02.00(07.14) | 0.61(0.12-3.09) | 0.375 | 0.345 |
| RVHD | 03.00(04.16) | 03.00(10.71) | 2.76(0.52-14.58) | 1.384 | 0.19 |
| COPD | 01.00 (01.38) | 02.00(07.14) | 5.385(0.46-61.92) | 1.966 | 1.00 |
| HIV | 02.00(02.77) | 01.00(03.57) | 1.29(0.11-14.89) | o.42 | 0.28 |
| CVA | 00.00 (00.00) | 01.00 (03.57) | Can't be calculated | 2.572 | 1.00 |
| OTHERS (IHD, alcoholism) | 03.00(04.16) | 01.00 (03.57) | 0.852(0.08-8.55) | 0.19 | |
| **Duration of disease** | 6.7 | 7.7 | | | NS |

**Table 2 --Correlation of clinical features for mortality outcome**

| Parameter | Survived + n=72(%) | Nonsurvived n= 28 (%) | Significant odds ratio 95% CI |
|---|---|---|---|
| Clinical symptoms and signs | | | |
| Fever | 70 (97.22) | 26(92.85) | 1.43-3.03 NS |
| Cough | 68(94.44) | 27(96.42) | 2.65-1.36 NS |
| Breathlessness | 64(88.88) | 22(78.57) | 0.54-1.87 NS |
| Throat pain | 23(31.94) | 10(35.71) | 1.08-0.70 NS |
| Bodyache | 14(19.44) | 03(10.71) | 0.53-1.69 NS |
| Hemoptysis | 08(11.11) | 02(07.14) | 0.95-1.82 NS |
| Vomiting | 08(11.11) | 03(10.71) | 1.24-1.37 NS |
| Diarrhoea | 06(08.33) | 01(03.51) | 1.01-2.30 NS |
| Rhinorrhoea | 18(25.00) | 08(28.57) | 0.98-0.89 NS |
| Chest pain Tachypnea | 04(05.55) | 01(03.51) | 1.37-2.60 NS |
| Rhonchi | 53(73.61) | 14(50.00) | 1.13-6.90 p <0.01 |
| crepitations | 10(13.88) | 03(10.71) | 0.91-1.55 NS |
| | 59(81.94) | 17(60.71) | 0.94-2.117 NS |

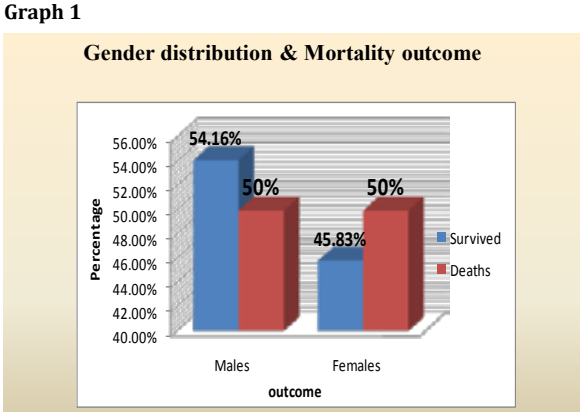
**Table 3 --Correlation of radiological parameters for mortality outcome**

| Radiological parameters | | Survived n=72(%) | Nonsurvived n=28(%) | P Value |
|---|---|---|---|---|
| Zonal involvement | | | | |
| RUZ | 38.88 | 71.42 | <0.001 | |
| LUZ | 27.77 | 35.71 | NS | |
| RMZ | 59.72 | 89.28 | <0.001 | |
| LMZ | 02.77 | 85.71 | <0.001 | |
| RLZ | 68.05 | 92.85 | <0.01 | |
| LLZ | 62.50 | 75.00 | NS | |
| Pattern | | | | |
| Consolidation | 59.72 | 57.14 | NS | |
| Reticulonodular | 22.22 | 21.42 | NS | |
| Nodular | 08.33 | 14.28 | NS | |
| Number of zones involved | | | | |
| 0 | 100.00 | 00.00 | NS | |
| 1 | 80.00 | 20.00 | NS | |
| 2 | 68.00 | 32.00 | NS | |
| 3 | 66.66 | 33.33 | NS | |
| 4 | 65.00 | 35.00 | NS | |
| 5 | 85.71 | 14.29 | NS | |
| 6 | 63.63 | 36.37 | NS | |

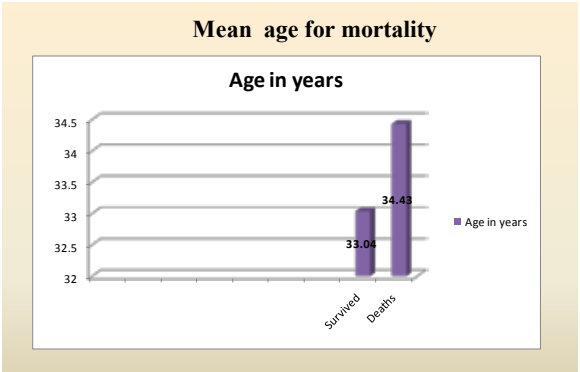
**Table 4 -Predictive role of lung zone affection in determination of outcome of disease**

| Lung segment affection | Outcome Cure/Death | | | |
|---|---|---|---|---|
| | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
| RUZ | 71 | 61 | 42 | 85 |
| LUZ | 36 | 72 | 34 | 74 |
| RMZ | 89 | 40 | 37 | 90 |
| LMZ | 86 | 47 | 39 | 90 |
| RLZ | 93 | 32 | 35 | 92 |
| LLZ | 75 | 38 | 32 | 79 |

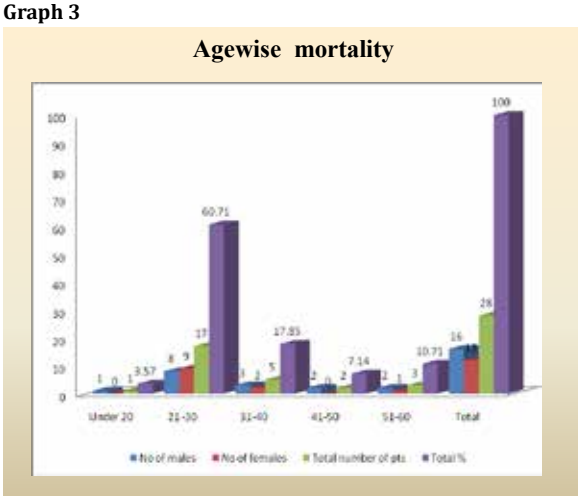
**Graph 1**



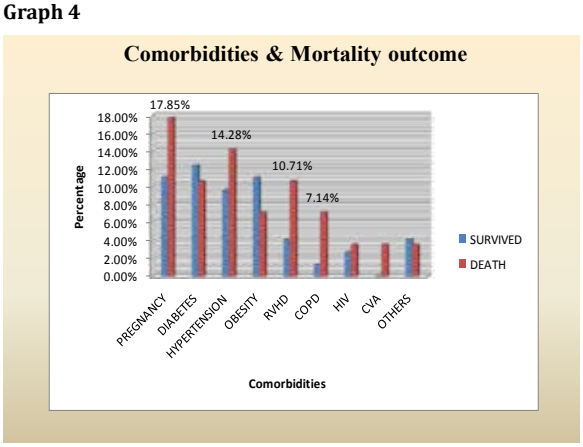

**Graph 2**



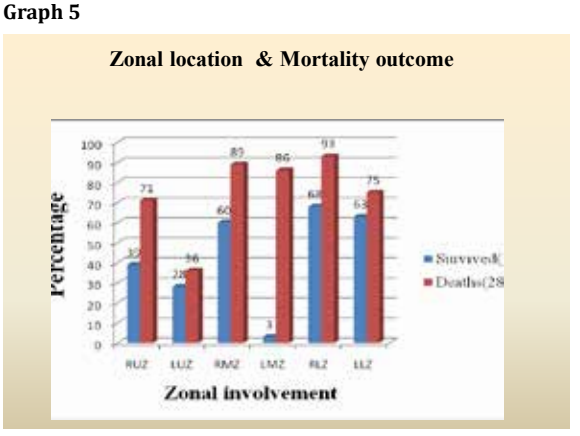

**Graph 3**




**Graph 4**




**Graph 5**



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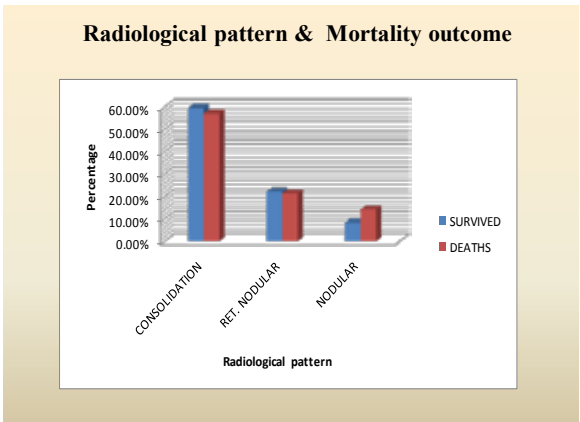
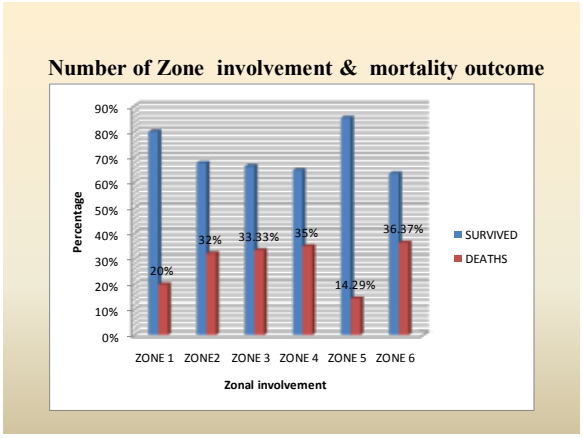
**Graph 6**




**Graph 7**

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