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# STUDY OF SECONADRY INFECTIONS AMONG PATIENTS ADMITTED IN A COVID ICU OF A TERTIARY CARE CENTRE IN CENTRAL INDIA

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## ABSTRACT

**Background -**. The prevalence incidence and characteristics of secondary infection in patients infected with Covid-19 is not well understood and has been raised as an important knowledge gap. Besides systemic effects of COVID-19 itself, the presence of secondary infections in such patients may have an adverse effect on patient's outcome and duration of stay in ICU. This study was hence planned to fill the knowledge gaps in regards to secondary infection in patients in COVID-19 ICU-their incidence, aetiology and effect on outcome.

**Material & Methods –** The present study was undertaken among Covid-19 patients admitted in ICU of Gandhi Medical College and Hamidia Hospital, Bhopal. Blood and urine samples of patients was taken on the day of admission in ICU and repeated on 3rd day if feasible and was sent for bacterial and fungal culture to determine the presence of secondary infection, causative organism and all patients were followed till discharge/death to determine the effect of secondary infection on outcome. All the data analysis was performed using appropriate statistical software (Epi Info Version-6).

**Results**

Out of 100 patients, 50.0% were females and 34.0% of the patients belonged to the age group of 56-70 years. 20 (80%) were males, while the rest 5 were females. Positive growth in blood was seen in 18 (54.5%) of the patients with secondary infection, while urine culture was positive in 11 (32.3%) patients. Both blood and urine culture were positive in 12.1% of the

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patients. Among the 40 isolates obtained from 33 patients with secondary infection, 8 (20.0%) patients had gram positive infections.

**Conclusion -.** Gram negative infections were common among the patients admitted in ICU. All efforts should be made to improve infection control practices. Strict practice of antimicrobial stewardship will help in reducing drug pressure, which is a key driver of drug resistance.

**Keywords** – COVID-19, Secondary Infections. Gram Negative

## INTRODUCTION

The coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first identified in December 2019 in Wuhan, China, and is currently circulating throughout the world[4]. The havoc created by COVID-19, and its associated morbidity and mortality is worth mentioning, By May 13, 2022, more than 517,648,631 cases have been diagnosed, and more than 6,261,708 deaths have been reported.[5]

Emerging evidence suggests that the number of patients with COVID-19 diagnosed with bacterial co-infections during hospitalization periods is rising. The source and specific nature of these infections are not explored fully[6-8]. Patients vulnerable to viral lung infections, such as influenza, SARS and COVID-19 are at the greatest risk to be co-infected with bacterial infections[6-10]. For example, the 2009 Swine Flu pandemic caused approximately 300,000 deaths around the world in which 30–55% of cases die of bacterial pneumonia[11-12]. It is now well documented that viral infections can weaken the host immunity, paving the way for the development of viral-bacterial co-infection[13-14]. The new coronavirus, COVID-19, is another example of this fact as most of the hospitalized patients with COVID-19 acquire a secondary bacterial infection during the course of stay or treatment[15-16].

The prevalence incidence and characteristics of secondary infection in patients infected with Covid-19 is not well understood and has been raised as an important knowledge gap. Besides systemic effects of COVID-19 itself, the presence of secondary infections in such patients may have an adverse effect on patient's outcome and duration of stay in ICU. This study was hence planned to fill the knowledge gaps in regards to secondary infection in patients in COVID-19 ICU-their incidence, aetiology and effect on outcome.

## MATERIAL AND METHODS

**Study Type:** Prospective (Hospital based) Observational Study

**Study Centre:** Department of Medicine Gandhi Medical College, & associated Hospitals (Hamidia Hospital) Bhopal.

**Study Duration:** January 2021 to May 2022

**Study Subjects**: Covid-19 patients admitted in ICU of Gandhi Medical College and Hamidia Hospital, Bhopal.

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**Methodology**

After approval of the study protocol by the Institutional Ethics Committee, written consent taken. The study was done in Department of Medicine, Gandhi medical collage & Hamidia hospital Bhopal to investigate secondary infection in patients admitted in Covid ICU. 100 patients aged 18 years and above giving consent were enrolled for the study. Blood sample and urine sample of patients was taken on the day of admission in ICU and repeated on 3rd day if feasible.

These blood and urine sample was sent for bacterial and fungal culture to determine the presence of secondary infection, causative organism and all patients were followed till discharge/death to determine the effect of secondary infection on outcome. Other relevant investigations were also sent during the due course. The findings of blood culture and urine culture at D1/2/3 was useful in pointing out the presence of secondary infection. Predilection on the basis of selected important demographic variables like age/sex in the development of secondary infections was also studied. Inflammatory markers like CRP, Procalcitonin and TLC was done to assess the severity of infection. Whether presence of comorbidities as well culture positivity has any role in outcome of patient admitted in Intensive Care Unit was studied. Role of elevated LFT and RFT values on the outcome of COVID-19 patients admitted in Intensive care Unit was also examined. All the relevant data was then entered in MS Excel

- **Inclusion criteria:** - Covid Positive patient with consent aged 18 years or more admitted in ICU.
- **Exclusion criteria:** -
    - Patient or attender not willing for consent
    - Communication impairment
- **Sample size:** 100 Patients

**Investigation**

- Blood Culture/Sensitivity for bacteria and fungi
- Urine Culture/sensitivity for bacteria and fungi
- CBC
- RFT
- LFT
- HbA1c
- Procalcitonin level

**Statistical analysis:**

All the data analysis was performed using appropriate statistical software (Epi Info Version-6). Frequency distribution and cross tabulation was used to prepare the tables. Quantitative variables were expressed as the mean and standard deviation. Categorical data was expressed as percentage. Microsoft office was used to prepare the graphs. Student t- test was used to

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compare the means. Chi Square test was used to compare the categorical data. P value of < 0.05 is considered as significant.

**RESULTS**

Half of the patients included in the study was males, while the other 50.0% were females. 34.0% of the patients belonged to the age group of 56-70 years followed by 31.0% from the age group of 26-40 years. Mean age of patients was found to be 48.11 years with a SD of 15.36.

66.0% had no comorbidities, while 15.0% had HTN, and 6.0% had DM. Both HTN and DM was observed in 13.0% of the participants. Figure 1 shows distribution of patients according to presence of secondary infection/Growth on culture during stay in hospital. 33% of patients showed presence of infection during stay in hospital Positive growth in blood was seen in 18 (54.5%) of the patients with secondary infection, while urine culture was positive in 11 (32.3%) patients. Both blood and urine culture were positive in 12.1% of the patients with secondary infections. Among 33 patients, 26 (78.8%) were having infection with single organism, while 7 (21.2%) had infection with more than one organism.

Table 1 shows the distribution of patients with secondary infection according to the etiology. Citrobacter was the predominant etiology followed Staphylococcus aureus. E coli and K pneumoniae was obtained in 7 (27.3%) and 6 (21.2%) patients respectively.

Among the 40 isolates obtained from 33 patients with secondary infection, 8 (20.0%) patients had gram positive infections, while the rest had gram negative infection. Citrobacter, Staph aureus and E coli were the predominant isolates.

Among 33 patients, 26 (78.8%) were having infection with single organism, while 7 (21.2%) had infection with more than one organism

Figure 2 shows the distribution of patients according to CRP levels and secondary infection. Among patients with secondary infection, 32 (97.0%) had elevated CRP levels and 56 (83.6%) patients without secondary infection also had elevated CRP levels. The distribution was found to be statistically insignificant.

Table 2 shows the distribution of patients according to D-dimer levels and secondary infection28 (84.8%) had elevated D-dimer levels and 53 (79.1%) patients without secondary infection also had elevated D-dimer levels. The distribution was found to be statistically insignificant

Table 3 describes that among patients with secondary infection, 30 (90.9%) had elevated procalcitonin levels and 45 (67.2%) patients without secondary infection also had elevated procalcitonin levels. The distribution was found to be statistically significant with a p value of less than 0.05

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Table 4 indicates that among the 33 patients with secondary infection, majority belonged to the age group of 56-70 years. 12 (36.4%) were from the age group of 26-40 years. Only 2 (6.1%) were above 70 years old.

According to Figure 3, among the 5 deaths happened in 33 patients with secondary infection, all 5 (100.0%) were due to gram negative organisms.

Among the total 33 patients who developed secondary infection, 28 were discharged. Among both groups of discharged and death patients, 75.0% in discharge group had no comorbidities. HTN and DM in combination was observed in 40.0% of the patients with secondary infection who succumbed to death, while HTN alone was the major factor common in individuals with secondary infection who got discharged.

## DISCUSSION

The present study entitled a study of secondary infections in patients admitted in COVID – ICU was carried out in Department of Medicine Gandhi Medical College, & associated Hospitals (Hamidia Hospital) Bhopal. This was a Prospective (Hospital based) Observational Study carried out between January 2021 to May 2022 among Covid-19 patients admitted in ICU of Gandhi Medical College and Hamidia Hospital, Bhopal. 100 patients aged 18 years and above giving consent were enrolled for the study.

In the present study, half of the patients included in the study was males, while the other 50.0% were females. 32 (84.21%) patients were male in the study undertaken by **Haocheng Zhang et.al[14] (2020). Marco Ripa et.al[15] (2021)** described in their study the gender distribution as having 67.9% males. 34.0% of the patients belonged to the age group of 56-70 years followed by 31.0% from the age group of 26-40 years. Mean age of patients was found to be 48.11 years with a SD of 15.36. The average age of enrolled patients was 64.76 years (SD 13.76) with 30 (78.95%) patients over 60 years old in the study by **Haocheng Zhang et.al[14] (2020).**

66.0% had no comorbidities, while 15.0% had HTN, and 6.0% had DM. Both HTN and DM was observed in 13.0% of the participants. Chronic diseases were noted in 24 (63.16%) patients in the study undertaken by **Haocheng Zhang et.al[14] (2020).** 46.8% of the patients in the study by **Marco Ripa et.al[15] (2021)** had history of CHD. Secondary infection in the form of growth in either urine or blood culture was witnessed in 33.0% of the patients. 22 (57.89%) patients developed secondary infections in the study by **Haocheng Zhang et.al[14] (2020)** and a microbiologically documented infection was diagnosed in 68/731 patients (9.3%) in the study undertaken by **Marco Ripa et.al[15] (2021).** In the study by **Sonam Vijay et.al[16] (2021)**, out of 17,534 admitted patients, 3.6% of patients developed secondary bacterial or fungal infection.

In the present study, among the 40 isolates obtained from 33 patients with secondary infection, 8 (20.0%) patients had gram positive infections, while the rest had gram negative infection.

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Distribution of patients with secondary infection according to the etiology shows that Citrobacter was the most common etiology in 9 (27.3%) patients, while staphylococcus aureus was responsible for infections in 8 (24.2%) patients. E coli was responsible for infections in another 18.2% patients followed by Enterococci in 12.1% patients as reported by **Haocheng Zhang et.al[14] (2020).** Gram-negative bacteria were isolated from 78% of patients. Klebsiella pneumoniae (29%) was the predominant pathogen, followed by Acinetobacter baumannii (21%). Thirty-five percent of patients reported polymicrobial infections, including fungal infections. High levels of carbapenem resistance were seen in A. baumannii (92.6%) followed by K. pneumoniae (72.8%) in the study carried out by **Sonam Vijay et.al[16] (2021)**.

Distribution of patients according to CRP levels and secondary infection shows that among patients with secondary infection, 32 (97.0%) had elevated CRP levels and 56 (83.6%) patients without secondary infection also had elevated CRP levels. The distribution was found to be statistically insignificant, while in the study undertaken by **Marco Ripa et.al[15] (2021)** baseline C-reactive protein (CRP) values were significantly different at baseline, procalcitonin was not significantly higher in patients who experienced a secondary infection. Levels of CRP at the time of the first secondary infection were significantly lower when compared to values at the time of the first microbiological specimen requested in patients with negative cultures.

Among 33 patients with secondary infection, 5 (15.2%) succumbed while in patients without secondary infection, 9 (13.4%) deaths were observed. In the study by **Haocheng Zhang et.al[14] (2020),** Patients without secondary infection had a significantly higher 60-day discharge rate improvement different from patients with secondary infection (P<0.001) Among 16 non-infection patients with severe and critical SARS-CoV-2 infection, 15 (93.75%) patients had discharged from the hospital within 60 days, and the median duration from ICU admission to discharge was 31 (IQR 27–39) days. 8 (36.36%) of 22 secondary infection patients had died by 60 days. Compared with non-infection patients, patients with secondary infection were more likely to receive invasive mechanical ventilation (86.36% (19/22) vs 25.00% (4/16), P < 0.0001). **Marco Ripa et.al[15] (2021)** described that among overall, 194/731 patients (26.5%) died: 30/68 (44.1%) with secondary infections and 164/663 (24.7%) without further infectious events (p 0.001). Median time to death after the first secondary infection was 9 days. Overall mortality among admitted COVID-19 patients, in these ten hospitals, was 11.6% (range 2.5%–45%), and mortality among COVID-19 patients with SIs was 56.7% (27%–78.9%). Mortality was higher in critically ill patients (in ICUs), ie 68% (313/459) as compared to patients in wards 27.6% (50/181) (p=0.0016).

There is a significant longer ICU stay and need of ventilation(P<0.001) for patients with secondary infection as described by **Astrid De Bruyn et.al[17] (2022).** Similar findings were observed in the present study as well.

## CONCLUSION

In conclusion, prevalence of bacterial and fungal infections in hospitalized Indian patients with COVID-19 is low; however, when such infections are present, they cause severe disease with worst outcomes. Gram negative infections were common among the patients admitted in

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ICU. These data were captured when the COVID-19 cases were on the rise, and the findings suggest that a lot of overprescribing of antimicrobials happened during that time. The practice of poor infection control and empirical over-use of broad-spectrum antimicrobials also provides fertile ground for future outbreaks with highly drug-resistant pathogens. Hence, all efforts should be made to improve infection control practices (like hand hygiene/ glove hygiene, device bundle compliance and air quality). This will help in reducing incidence of secondary infections, particularly those of nosocomial origin. Strict practice of antimicrobial stewardship will help in reducing drug pressure, which is a key driver of drug resistance.

**Figure 1 - Distribution of patients according to presence of secondary infection/Growth on culture during stay in hospital**

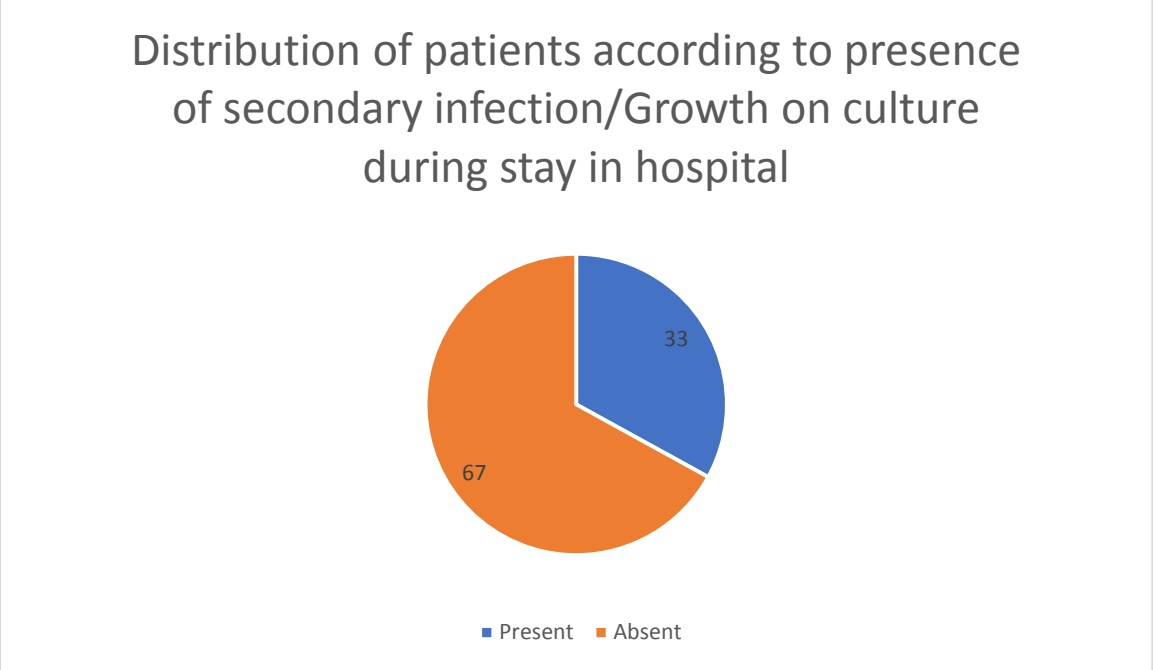


**Table 1 - Distribution of patients with secondary infection according to the etiology (Multiple responses)**

| S No | Organism | Frequency | Percentage |
|---|---|---|---|
| 1 | Staphylococcus aureus | 8 | 24.2 |
| 2 | Citrobacter | 9 | 27.3 |
| 3 | E-coli | 7 | 21.2 |
| 4 | K pneumoniae | 6 | 18.2 |
| 5 | Enterococci | 4 | 12.1 |
| 6 | Acinetobacter | 2 | 6.1 |
| 7 | K oxytoca | 2 | 6.1 |
| 8 | Pseudomonas | 1 | 3.0 |
| 9 | Candida | 1 | 3.0 |

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**Figure 2 - Distribution of patients according to CRP levels and secondary infection**

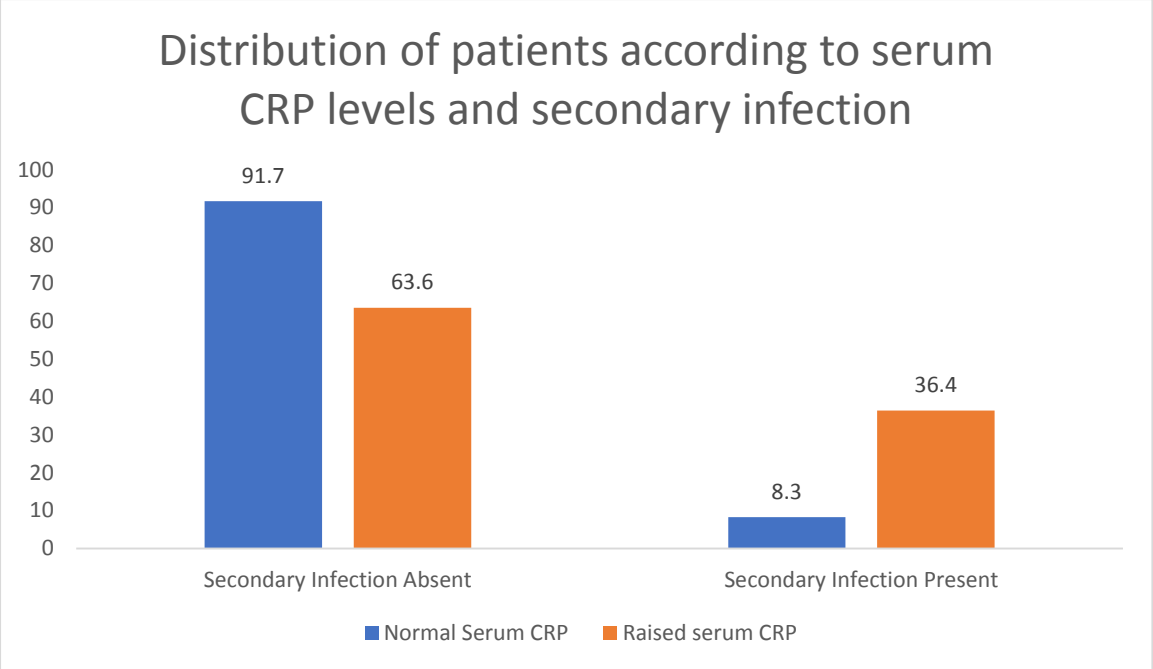


**Table 2 - Distribution of patients according to D-dimer levels and secondary infection**

| D-dimer | Secondary Infection | | Total | Chi Square value<br>P value |
|---|---|---|---|---|
| | Absent | Present | | |
| | N (%) | N (%) | N (%) | 0.474 |
| Normal | 14 (20.9) | 5 (15.2) | 19 (19.0) | |
| High | 53 (79.1) | 28 (84.8) | 81 (81.0) | 0.491 |
| Total | 67 (100.0) | 33 (100.0) | 100 (100.0) | |

**Table 3 - Distribution of patients according to serum pro calcitonin levels and secondary infection**

| Procalcitonin | Secondary Infection | | Total | Chi Square value<br>P value |
|---|---|---|---|---|
| | Absent | Present | | |
| | N (%) | N (%) | N (%) | 6.649 |
| Normal | 22 (32.8) | 3 (9.1) | 25 (25.0) | |
| High | 45 (67.2) | 30 (90.9) | 75 (75.0) | 0.010 |
| Total | 67 (100.0) | 33 (100.0) | 100 (100.0) | |

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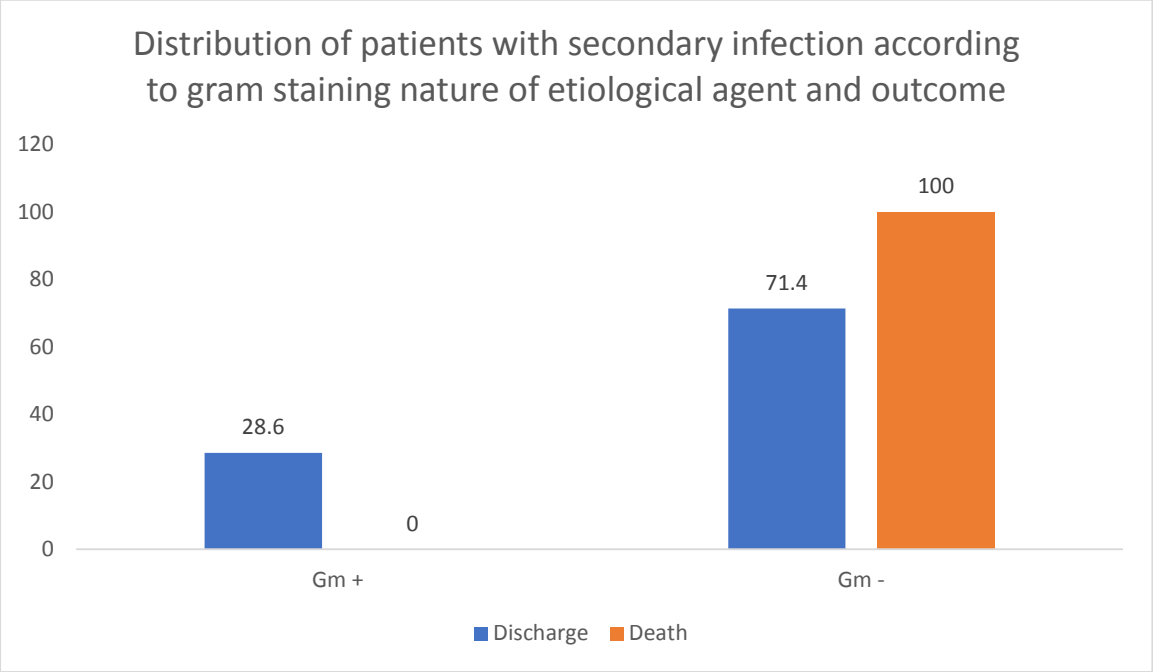
**Table 4 - Distribution of patients according to age group in years and presence of secondary infection**

| Age group | Secondary Infection | | Total | Chi Square value<br>P value |
|---|---|---|---|---|
| | Absent | Present | | |
| | N (%) | N (%) | N (%) | 5.618<br><br>0.230 |
| ≤25 | 5 (7.5) | 3 (9.1) | 8 (8.0) | |
| 26-40 | 19 (28.4) | 12 (36.4) | 31 (31.0) | |
| 41-55 | 20 (29.9) | 3 (9.1) | 23 (23.0) | |
| 56-70 | 21 (31.3) | 13 (39.4) | 34 (34.0) | |
| >70 | 2 (3.0) | 2 (6.1) | 4 (4.0) | |
| Total | 67 (100.0) | 33 (100.0) | 100 (100.0) | |

**Figure 3– Distribution of patients with secondary infection according to gram staining nature of etiological agent and outcome**

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