Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.47750/jptcp.2023.30.15.053

Human epidermal growth factor receptor 2 (Her2/Neu) immunoexpression in gastrointestinal adenocarcinomas: A clinicopathological study

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Submitted: 23 April 2023; Accepted: 16 May 2023; Published: 13 June 2023

ABSTRACT

One of the major causes of cancer-related mortality is gastrointestinal (GI) cancer. The outcomes of surgical resection of advanced cancer are still poor, despite the fact that it has improved the overall prognosis of patients with these malignancies. As a consequence, it is essential to look for predictors of disease survival and therapeutic response. The current study was conducted with the aims to study the clinicopathological parameters, to study HER2 /neu expression and to look out the association between the expression of HER2/neu and other clinicopathological parameters like age, gender, tumor location (whether gastric/gastro esophageal junction), histological pattern (Laurens classification), grade and stage of adenocarcinomas. A total of 100 cases of GI adenocarcinoma were studied for a period of 6 years (retrospective and prospective) in ESI PGIMSR, Bangalore. IHC analysis for HER2neu was performed and the association of immune expression markers were studied with clinicopathological and prognostic markers. Gastric Adenocarcinomas were seen mostly in the age group of 41-50yrs and more in male population and colorectal in the age group of 51-60yrs and in female population. Diffuse type in gastric adenocarcinomas and mucinous type in colorectal adenocarcinomas were the most common type in our study. Among Gastric adenocarcinomas, majority were poorly differentiated and in colorectal adenocarcinomas moderately differentiated are

the most common type. There was direct correlation between the presenting symptoms among the gastric and colorectal adenocarcinomas (<0.04%). Overall, Her2neu positivity was found in 39.6% of gastric adenocarcinomas and 17.3% of colonic adenocarcinomas. In general, GI Adenocarcinomas showed stronger Her2neu positivity in comparison to colorectal carcinomas. Her2neu positivity correlated with the type of gastro-esophageal carcinomas (p<0.03%). The present study emphasizes the role of Her2 expression in Gastro intestinal adenocarcinomas in quantifying the subset of patients that could benefit from targeted therapy, thereby improving clinical outcome in these patients.

Keywords: *Gastric adenocarcinoma; colorectal adenocarcinomas; Her2neu; IHC; age; site; TNM STAGE*

INTRODUCTION

Globally, cancer is a serious health issue. The frequency of gastrointestinal (GI) pregnancies varies geographically and is influenced by nutritional, socioeconomic, and genetic variables (Al-Mhanna, Ghazali et al., 2022, Kalyani, Das et al., 2010). For cancer research and healthcare planning, it is crucial to monitor historical patterns and incidence (Ahmed, Ali et al., 2020). The most effective way to assess the prevalence of cancer in the general population is via cancer registries (Ahmad, Baig et al., 2022, Ahmed, Abusalah et al., 2022, Bouvier, Remontet et al., 2004, Dhakras, Uboha et al., 2020).

The Her2 (also called Erb-B2) is a proto-oncogene located on chromosome 17q21 and possess tyrosine kinase activity (Kumar, Abbas et al., 2010, Liu, Sethi et al., 2018). It is overexpressed or amplified in a range of other tumour such as that of gastro oesophageal junction, gastric, intestinal, bladder, lung, breast, prostate, bladder, ovary, fallopian tubes, endometrium and colon (Kountourakis, Pavlakis et al., 2006, Schoppmann, Jesch et al., 2010). The Her 2neu data over expression in gastroesophageal cancer varies widely from 9 to 60%. It correlates with tumour invasion, nodal metastasis and is indicative of poor prognosis. In gastric tumours, intestinal type is more likely to be Her2neu positive than diffuse/mixed (Gravalos and Jimeno, 2008, Hao, Foong et al., 2016, Huisman and Kellenberger, 2008).

Globally nearly 800,000 colorectal cancer cases are believed to occur each year, which account for approximately 10% of all cancers (Bukhari, Naveed et al., 2021, Kong, Li et al., 2021). In India, GI cancer ranks fifth among male cancer deaths and sixth among female cancer deaths (Jain, Wadhwa et al., 2022). Although rigorous surgical resection has improved the overall prognosis of patients with these malignancies, surgical resection for advanced cancer still produces poor outcomes, necessitating the need to identify predictors of disease survival and therapeutic response (Lin, He et al., 2018, Rosai, 2011). Apart from various prognostic factors including the clinical features, tumour histopathology, tumour grade, lymph node status, and stage of the tumour, considerable interest has focused on identification of novel tumour-based markers which can more accurately predict the prognosis (Mohd Salim, Mussa et al., 2023, Mussa, Mohd Idris et al., 2022, Rosenbaum and Gonzalez, 2021). The etiology of colorectal and gastric cancers is complex, involving an interplay of environmental and genetic factors (Ohmi, Ohno et al., 2021). They develop through a multistep process characterised by histopathologic precursor lesions and molecular genetic alterations involving APC, K-ras and p53 genes (De Carli, ROCHA et al., 2015). The Her2neu data over expression in gastroesophageal cancer varies widely from 9 to 60% (PRABHA, BANTUMILLI et al., 2022). It correlates with tumor invasion, nodal metastasis and is indicative of poor prognosis (Hu, Bandla et al., 2011, JACOBSON, CRAWFORD et al., 2009).

Trastuzumab along with chemotherapy is considered as a new treatment option for patient with Her2 positive advanced cancer (Gravalos and Jimeno, 2008, Huisman and Kellenberger, 2008, Kountourakis, Pavlakis et al., 2006). The current study was conducted with the objectives to study the clinicopathological profiles, to study HER2 /neu expression and to find the association between the expression of HER2/neu and other clinicopathological parameters like age, gender, tumor location (whether gastric /gastro oesophageal junction), histological pattern (Laurens classification), grade and stage of Adenocarcinomas of GIT.

MATERIALS AND METHODS

This was a retrospective study conducted by the Department of Pathology, Employees' state insurance corporation, Medical College & Post Graduate Institute of Medical Sciences & Research (ESICMC & PGIMSR), Ministry of Labour, Govt. of India, Rajajinagar, Bangalore. This study included all primary adenocarcinomas of the oesophagus, stomach, small intestine, large intestine specimens and biopsies for a period of 6 years. Demographic profile of the patients such as age and gender were retrieved from archives file of department of pathology, ESICMC & PGIMSR. For prospective study (January, 2018 to June, 2019), cases received in the department of pathology during the period were taken. The carcinomas of the oral cavity, oropharynx and salivary glands and all the other malignancies other than the adenocarcinomas of the GI tract were excluded.

Sample collection

A total of 100 cases was studied with data collection being retrospective and prospective. for retrospective study, archived cases was collected along with clinicopathological details. The required clinicopathological details in retrospective cases was collected from the department files and medical records department of institution.

For prospective study a thorough gross examination of resected specimens was done carefully to detect any abnormalities. Representative sections from any identifiable lesion were submitted. The entire specimen was submitted for microscopic examination. Complete clinicopathological details as per the proforma was collected.

Formalin fixed paraffin embedded sections of both archived and prospective cases was stained with H&E stain and were studied histopathological. The patient's medical records were retrieved to obtain patients clinicopathological parameters including age at diagnosis, sex, endoscopy findings, tumour location and histological classification. histological classification was determined according to WHO and LAURENS classification.

IHC was performed by manual method. primary pre-diluted antibody (biogenex) (Rabbit IgG Antibody clone EP1045Y) was used.

The immunostained slides were examined for weak/strong, complete/incomplete membrane staining for Her2neu. Depending upon proportion of positively stained tumor cells. Her2neu IHC for biopsy and resected specimens was categorised as negative, equivocal and positive. The Immunohistochemistry slides were scored according to scoring system by Hoffman et al., (2008) (Hofmann, Stoss et al., 2008).

Statistical analysis

Descriptive statistics using proportion, mean, SD and percentage was used to describe the data. Chi-square tests was used to proportion in the different groups. Level of significance was fixed at 95%.

RESULTS

During the study period 100 cases of GI adenocarcinomas were studied in the department of pathology ESIC & PGIMSR over a period of 6 yrs. All cases were studied histopathologically and evaluated for HER2neu expression using IHC. The age in both gastric and colorectal carcinoma cases was ranging from 31 to 80 yrs. The maximum cases seen in gastric carcinoma seen in the range of 41-50 yrs. (33.3%) and minimum in the age range of 31-40 yrs. (6.3%). (Table 1)

TABLE 1: Distribution of gastric and colorectal carcinoma according to the age groups.

Variable	Category	Gastric		Colorectal		χ2 Value	P-Value
		n	%	N	%		
Age (Years)	31-40	3	6.3%	4	7.7%	2.820	0.590
	41-50	16	33.3%	10	19.2%		
	51-60	15	31.3%	21	40.4%		
	61-70	10	20.8%	11	21.2%		
	71-80	4	8.3%	6	11.5%		
Gender	Males	30	62.5%	24	46.2%	2.685	0.10

	Females	18	37.5%	28	53.8%		

The maximum age seen in colorectal carcinoma cases is in the age range of 51-60 yrs. (40.4%) and minimum age range from 31-40 yrs. (7.7%). In gastric carcinomas Males were predominant whereas in colorectal carcinomas females were predominant.

For gastric carcinoma pain abdomen (39.6%) followed by altered bowel habits (12.5%) and dyspepsia (12.5%) and for colorectal carcinoma pain abdomen (46.2%) followed by bleeding per rectum (34.6%) were the predominant symptoms. It was statistically significant (<0.001). (Table 2)

TABLE 2: Comparison of presenting symptoms among Gastric and Colorectal cases using Chi Square Test. Showing significant relationship between the presenting symptoms among the gastric and colorectal cases.

Variable	**Category**	**Gastric**		**Colorectal**		**χ2-value**	***p*-value**
		n	**%**	***n***	**%**		
Symptoms	Acute Intestinal Obstruction	0	0.0%	2	3.8%	40.286	< 0.001*
	Altered Bowel Habits	6	12.5%	6	11.5%		
	Bleeding per rectum	0	0.0%	18	34.6%		
	Dyspepsia	6	12.5%	0	0.0%		
	Dysphagia	3	6.3%	0	0.0%		
	Pain Abdomen	19	39.6%	24	46.2%		
	External Haemorrhoids	1	2.1%	1	1.9%		
	Gastric Outlet Obstruction	3	6.3%	0	0.0%		
	Recurrent Vomiting	6	12.5%	0	0.0%		
	Wt. Loss / Fatiguability	4	8.3%	1	1.9%		

*Showing significant relationship between the presenting symptoms among the gastric and colorectal cases.

The most common site of gastric carcinoma was Antrum (18.8%), whereas in colorectal carcinoma was rectum (36.5%) followed by transverse colon (12.5%). The most common type of gastric carcinoma is diffuse type (Figure 1), in colorectal carcinoma mucinous type of Adenocarcinomas was seen (46.2%) (Figure 2 and Table 3)

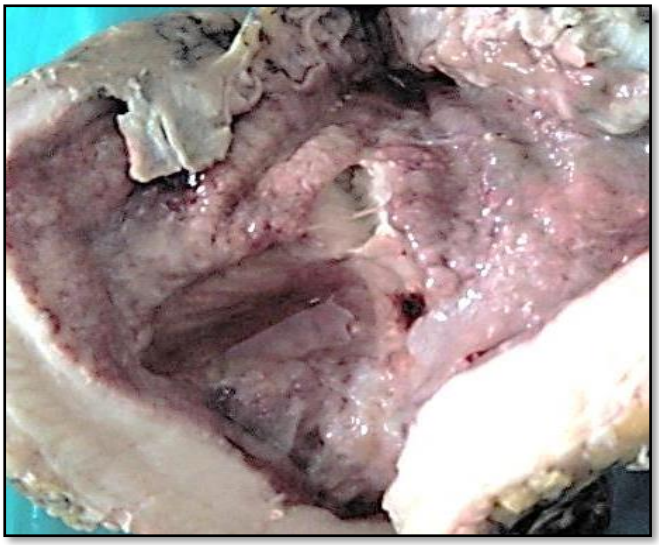

FIG 1: Gastrectomy. Cut surface: Diffuse thickening of the entire stomach wall with whitish glistening areas in a case of Linitis plastica (diffuse gastric adenocarcinoma).

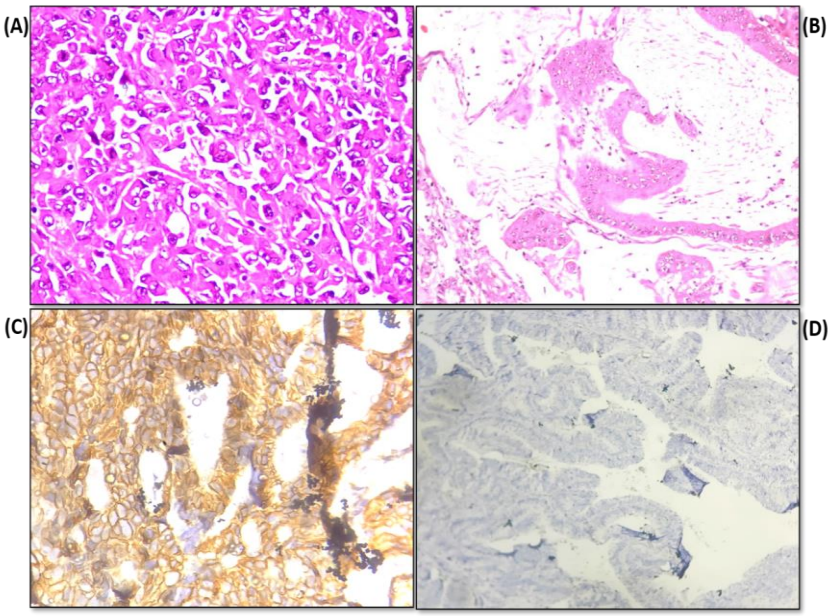

FIG 2: (A): Diffuse type of adenocarcinoma of stomach (H&E x40X). (B): Mucinous adenocarcinoma of colon (H&E ,10X). (C): HER2NEU 3+ positivity in Moderately differentiated adenocarcinoma -Gastro Oesophageal junction (IHC x40x). (D): Negative in well diff Adenocarcinoma-Colon (IHC x40x).

TABLE 3: Site of tumor in the cases of gastric carcinoma and in colorectal carcinoma.

Variable	Sites	n	%
Gastroesophageal Carcinoma Cases (n=48)			
Site of Tumor	Body	7	14.6%
	Antrum	9	18.8%
	Cardia + Body	1	2.1%
	Entire Stomach	5	10.4%
	Fundus + Body	4	8.3%
	Gastroesophageal Junction	5	10.4%
	Pre-pyloric	1	2.1%
	Pyloric Antrum	6	12.5%
	Pylorus	4	8.3%
	Greater curvature	1	2.1%
	Lesser Curvature	5	10.4%
Colorectal Carcinoma Cases (n=52)			
Site of Tumor	Ascending Colon	4	7.7%
	Caecum	1	1.9%
	Caecum+Asc. Colon	4	7.7%
	Hepatic Flexure	2	3.8%
	Ileocaecum	2	3.8%
	Rectosignmoid	3	5.8%
	Rectum	19	36.5%
	Rectum+Anal canal	2	3.8%
	Sigmoid colon	6	11.5%
	Sigmoid colon+Rectum	2	3.8%
	Transverse colon	06	12.5%
	Descending colon	1	1.9%

In gastric carcinoma majority presented with Grade III (poorly differentiated tumours, 43.8%) and stage 2 (26.3%). In colorectal adenocarcinomas majority were Grade 2 (moderately differentiated, 46.2%) and stage 2a (27.8%). On statistical correlation no correlation was seen between the tumour grade, stage and age in both gastric and colorectal adenocarcinomas.

Semiquantitative analysis of HER2NEU immunohistochemisty

19 (39.6%) cases of Gastric carcinoma showed HER2neu positivity, whereas 20 (41.7%) cases were negative. In colorectal carcinomas only 9 (17.3%) cases were positive, and majority 32 (61.5%) cases were negative. There was significant association between the her2neu immunostaining in colorectal adenocarcinomas (p<0.04%). (Table 4)

TABLE 4: Comparison of her 2 neu final immunostaining results among Gastric and Colorectal cases.

Variable	Category	Gastric		Colorectal		c2 Value	*p*-value
		n	%	N	%		
her 2 Final Result	Positive	19	39.6%	9	17.3%	6.391	0.04* (significant)
	Negative	20	41.7%	32	61.5%		
	Equivocal	9	18.8%	11	21.2%		

*Statistically significant.

Among Gastric carcinoma 9 cases of intestinal (60%), 4 (20%) cases of diffuse, and signet ring cell type (60%) showed HER2NEU positivity. It was statistically significant (p<0.03%). Among colorectal adenocarcinomas 25% cases of signet ring cell type, 12.5% of mucinous type showed HER2neu positivity where as 30% papillary cases showed Equivocal positivity. In both gastro Oesophageal (41.7%) and colorectal adenocarcinomas (25%) moderately differentiated tumours showed major Her2neu positivity. Among gastric carcinomas, majority (50%) showed positivity in stage 4 tumours. Whereas in colorectal carcinomas stage 3b showed major positivity. There was no direct correlation between Her2neu and age, site, stage and grade of both the gastric and colorectal adenocarcinomas. (Table 5)

TABLE 5: Result of her2neu Immmunostaining in relation to the TNM stage in gastric carcinoma and colorectal carcinoma.

Grades	Positive		Negative		Equivocal		c2 Value	*P*-Value
	n	%	n	%	n	%		
Gastroesophageal Carcinoma								
Stage 1	0	0.0%	0	0.0%	0	0.0%	9.788	0.64
Stage 1a	1	33.3%	1	33.3%	1	33.3%		
Stage 1b	1	50.0%	1	50.0%	0	0.0%		
Stage 2	0	0.0%	3	60.0%	2	40.0%		
Stage 2a	0	0.0%	1	50.0%	1	50.0%		
Stage 3	0	0.0%	1	100.0%	0	0.0%		
Stage 3a	0	0.0	2	100.0%	0	0.0%		
Stage 3b	0	0.0%	0	0.0%	0	0.0%		
Stage 4	2	50.0%	2	50.0%	0	0.0%		
Colorectal Carcinoma								
Stage 1	0	0.0%	3	100.0%	0	0.0%	14.833	0.14
Stage 1a	0	0.0%	1	100.0%	0	0.0%		
Stage 1b	0	0.0%	0	0.0%	0	0.0%		

Stage 2	0	0.0%	3	100.0%	0	0.0%		
Stage 2a	0	0.0%	2	40.0%	3	60.0%		
Stage 3	0	0.0%	0	0.0%	0	0.0%		

DISCUSSION

In the present study, total 100 cases of gastrointestinal tumors were studied, indicating frequency of HER2/ neu over expression. 48 cases of gastric carcinoma and 52 cases of colorectal carcinomas were studied which is comparable to other studies. The age in both gastric and colorectal adenocarcinomas was ranging from31-80 years which correlates with the findings of other authors. Thus, elderly age group is a risk factor for the development of adenocarcinomas.

In the present study the number of gastric biopsies and specimens in gastric adenocarcinomas were 61% and 39%which was compared to Gupta et al., (Gupta, Gaddam et al., 2012) study where biopsy was 63.6% and specimen 36.3%. Rajgopal et al., (Rajagopal, Niveditha et al., 2015) has 73.3% biopsies and 26.6% specimens. The number of colorectal biopsies and specimens in our study were 65.3% and 34.6% respectively. The males outnumbered the females in our study which is compared to other studies as well such as Gupta et al., (Gupta, Gaddam et al., 2012), and Rajgopal et al., (Rajagopal, Niveditha et al., 2015). In the present study Diffuse type (62.5%) in case of gastric adenocarcinoma and mucinous type (46.2%) in case of colorectal adenocarcinomas were studied. Rajgopal et al., (Rajagopal, Niveditha et al., 2015) showed intestinal type of gastric adenocarcinoma. Seyed-Hamid Madani et al., (Madani, Rahmati et al., 2015) showed 95%of NST type of colorectal adenocarcinoma.

Current study study showed Grade 1-20.8%, Grade 2-35.4%, Grade 3-43.8% in Gastric adenocarcinoma. Whereas Rajgopal et al., (Rajagopal, Niveditha et al., 2015) showed Grade 1-15%, Grade 2- 66.6%, Grade 3- 18.3% respectively. Gupta et al., (Gupta, Gaddam et al., 2012) showed Grade 1-11.8%, Grade 2-31.8%, Grade 3- 8.18%. The most common site is antrum which Rajgopal et al., (Rajagopal, Niveditha et al., 2015) also showed the similar results. In present study colorectal adenocarcinomas showed Grade 1 -38.5%, Grade 2-46.2%, Grade 3- 15.4%, which was comparable with other studies. The most common stage is stage 2a [27.8%].

Her 2 neu positivity (3+) was significantly higher (50%) in low grade gastric cancer and lower (14.5%) in high grade gastric cancer. Her 2 neu score was seen higher in females and in the age group less than 60 years. Her2neu positivity was seen in Laurens intestinal type of adenocarcinomas which can be correlated with present study. Also seen in stage 3C. However. there was no significant difference between Her2neu overexpression and other variables. In the present study Her2neu positivity was seen in 28 out of 48(58.3%) cases of gastric adenocarcinomas. 11 cases (22.9%) showed zero, 9 cases (18.8%) showed 1+, 9 cases (18.8%) showed 2+ (equivocal) and 19 cases (39.6%) showed 3+ positivity. This was statistically significant. 66.7% positivity is seen in the age range of 31-40 years. 100% positivity is seen in cardia and body. 55.6% positivity is seen in 10 cases of intestinal type. Among tumour grades 8 cases (47.1%) were moderately differentiated. Among staging 50% positivity is seen in stage 1b and stage 4.

Rajgopal et al., (Rajagopal, Niveditha et al., 2015) showed HER2 expression in 26.7% of tumors, predominantly in males and in intestinal type. In this study Her2neu expression correlated with the tumour grade (p<0.04). whereas in our study there was no such correlation. Gupta et al., (Gupta, Gaddam et al., 2012) performed a study on a total 110 cases. Her2 neu positivity was seen in 27 cases (24.5%). Proximal tumours showed slightly higher Her2neu expression as compared to the distal part which correlated with our study. However, there was no significant correlation or association between her2neu and age, sex, site. In this present study also, it was no statistically significant.

In the present study, out of 52 cases 9 cases (17.3%) showed positive,32 cases 61.5% showed negative and 11 cases (21.2%) showed equivocal positive. This was statistically significant (<0.04). HER2neu positivity was seen more in the age group of 51-60 yrs. The site where Her2neu showed 100% positivity was caecum. According to WHO classification 25% positivity

seen in the signet ring cell carcinoma. Moderately differentiated followed by poorly differentiated showed 25% positivity. The most common stage group seen is stage 3b. There was no significant correlation between Her2neu positivity and the age, sex, site, grade and stage of the tumour. Also, there is no correlation between Her2 neu and other variables such as age, gender and grade which correlated with our study.

Sayadnejad et al., (Sayadnejad, Firouzjahi et al., 2017) performed Her2neu on all 50 cases of colorectal carcinoma. 76% were negative and 12 cases (24%) showed Her2neu positivity. Most of the Her 2 neu positive cases were female. There was no significant correlation between sex, Her2 neu positive cases, Grade and site of the tumour. Madani et al., (Madani, Rahmati et al., 2015) surveyed 211 cases out of which 26 cases (12.3%) showed 3+positivity, 75 cases (35.5%) were equivocal negative were 19.9%. There is a correlation between Her2neu scores and differentiation most score 3+ cases being well differentiated ($p<0.05$).

CONCLUSIONS

The GI and colorectal adenocarcinomas are two of the most common malignancies causing death worldwide. Because of their late presentations especially in the developing countries, prognosis is not very good. These carcinomas feature a high number of genetic changes, many of which have potential prognostic predictive value. Some forecast the chance that a patient would benefit from a particular therapy, while others give treatment independent information on patient survival. Given that a significant portion of patients have Her2neu protein overexpression, it seems that EGFR mutation is crucial in the emergence of gastric and colorectal cancer. The present study emphasizes the role of HER2 expression in GI Adenocarcinomas, in quantifying the subset of patients that could benefit from targeted therapy, thereby improving clinical outcome in these patients.

Author Contributions

Conceptualization, A., S.L.B., and S.M.V.; methodology, A., S.L.B., and S.M.V.; software, A.A.R., H.A., and A.A.A.; validation, S.A.A., A.A., and S.A.; formal analysis, A., S.L.B., and S.M.V.; investigation, A., S.L.B., and S.M.V.; resources, A.A.R., H.A., and A.A.A.; data curation, A., S.L.B., and S.M.V.; writing—original draft preparation, M.A., H.A., A.A.A., and S.A.A.; writing—review and editing, A.A.R., S.A., and A.A.; visualization, N.A.; supervision, S.L.B., and S.M.V.; project administration, A. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Employees' state insurance corporation, Medical College & Post Graduate Institute of Medical Sciences & Research. Ministry of Labor, Govt. of India. (Protocol code: No. 532/11/12/Ethics/ESICMC&PGIMSR/Estt. Vol. III approved on 21/11/2017).

Informed Consent Statement

As it was a retrospective study, the informed consent of data from all subjects involved in the study was waived off. Written informed consent has been obtained from the hospital in-charge to publish this paper.

Data Availability Statement

All data reported to this study has been reported in the manuscript.

ACKNOWLEDGMENTS

Authors would like to acknowledge Naveed Ahmed for his extensive guidelines in the current study.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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