Gallbladder Stones in Children
Case Report and Review of Literature

Diseases
Cancer, Ophthalmology & Pediatric

Cervical and Vaginal Specimens
Cox-Proportional Hazard (CPH) Model

Discovering Thoughts, Inventing Future

© 2001-2021 by Global Journal of Medical Research, USA
<table>
<thead>
<tr>
<th>Editorial Board</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dr. Apostolos Ch. Zarros</strong></td>
<td><strong>Dr. William Chi-shing Cho</strong></td>
</tr>
<tr>
<td>DM, Degree (Psychio) holder in Medicine, National and Kapodistrian University of Athens MRes, Master of Research in Molecular Functions in Disease, University of Glasgow FRNS, Fellow, Royal Numismatic Society Member, European Society for Neurochemistry Member, Royal Institute of Philosophy Scotland, United Kingdom</td>
<td>Ph.D., Department of Clinical Oncology Queen Elizabeth Hospital Hong Kong</td>
</tr>
<tr>
<td><strong>Dr. Alfio Ferlito</strong></td>
<td></td>
</tr>
<tr>
<td>Professor Department of Surgical Sciences University of Udine School of Medicine, Italy</td>
<td></td>
</tr>
<tr>
<td><strong>Dr. Jixin Zhong</strong></td>
<td></td>
</tr>
<tr>
<td>Department of Medicine, Affiliated Hospital of Guangdong Medical College, Zhanjiang, China, Davis Heart and Lung Research Institute, The Ohio State University, Columbus, OH 43210, US</td>
<td></td>
</tr>
<tr>
<td><strong>Rama Rao Ganga</strong></td>
<td></td>
</tr>
<tr>
<td>MBBS MS (University of Health Sciences, Vijayawada, India) MRCS (Royal College of Surgeons of Edinburgh, UK) United States</td>
<td></td>
</tr>
<tr>
<td><strong>Dr. Izzet Yavuz</strong></td>
<td></td>
</tr>
<tr>
<td>MSc, Ph.D., D Ped Dent. Associate Professor, Pediatric Dentistry Faculty of Dentistry, University of Dicle Diyarbakir, Turkey</td>
<td></td>
</tr>
<tr>
<td><strong>Sanguansak Rerksuppaphol</strong></td>
<td></td>
</tr>
<tr>
<td>Department of Pediatrics Faculty of Medicine Srinakharinwirot University NakornNayok, Thailand</td>
<td></td>
</tr>
<tr>
<td><strong>Dr. Michael Wink</strong></td>
<td></td>
</tr>
<tr>
<td>Ph.D., Technical University Braunschweig, Germany Head of Department Institute of Pharmacy and Molecular Biotechnology, Heidelberg University, Germany</td>
<td></td>
</tr>
<tr>
<td><strong>Dr. Pejcic Ana</strong></td>
<td></td>
</tr>
<tr>
<td>Assistant Medical Faculty Department of Periodontology and Oral Medicine University of Nis, Serbia</td>
<td></td>
</tr>
<tr>
<td><strong>Dr. Ivandro Soares Monteiro</strong></td>
<td></td>
</tr>
<tr>
<td>M.Sc., Ph.D. in Psychology Clinic, Professor University of Minho, Portugal</td>
<td></td>
</tr>
<tr>
<td><strong>Dr. Sanjay Dixit, M.D.</strong></td>
<td></td>
</tr>
<tr>
<td>Director, EP Laboratories, Philadelphia VA Medical Center Cardiovascular Medicine - Cardiac Arrhythmia Univ of Penn School of Medicine Web: pennmedicine.org/wagform/MainPage.aspx?</td>
<td></td>
</tr>
<tr>
<td><strong>Antonio Simone Laganà</strong></td>
<td></td>
</tr>
<tr>
<td>M.D. Unit of Gynecology and Obstetrics Department of Human Pathology in Adulthood and Childhood “G. Barresi” University of Messina, Italy</td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>Title/Professional Affiliation</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Dr. Han-Xiang Deng          | MD, Ph.D.  
Associate Professor and Research Department  
Division of Neuromuscular Medicine  
Davee Department of Neurology and Clinical Neurosciences  
Northwestern University Feinberg School of Medicine  
Web: neurology.northwestern.edu/faculty/deng.html |
| Dr. Pina C. Sanelli         | Associate Professor of Radiology  
Associate Professor of Public Health  
Weill Cornell Medical College  
Associate Attending Radiologist  
NewYork-Presbyterian Hospital  
MRI, MRA, CT, and CTA  
Neuroradiology and Diagnostic Radiology  
M.D., State University of New York at Buffalo, School of Medicine and Biomedical Sciences  
Web: weillcornell.org/pinasanelli/ |
| Dr. Roberto Sanchez         | Associate Professor  
Department of Structural and Chemical Biology  
Mount Sinai School of Medicine  
Ph.D., The Rockefeller University  
Web: mountsinai.org/ |
| Dr. Michael R. Rudnick      | M.D., FACP  
Associate Professor of Medicine  
Chief, Renal Electrolyte and Hypertension Division (PMC)  
Penn Medicine, University of Pennsylvania  
Presbyterian Medical Center, Philadelphia  
Nephrology and Internal Medicine  
Certified by the American Board of Internal Medicine  
Web: uphs.upenn.edu/ |
| Dr. Feng Feng               | Boston University  
Microbiology  
72 East Concord Street R702  
Duke University  
United States of America |
| Dr. Seung-Yup Ku            | M.D., Ph.D., Seoul National University Medical College, Seoul, Korea Department of Obstetrics and Gynecology  
Seoul National University Hospital, Seoul, Korea |
| Dr. Hrushikesh Aphale       | MDS- Orthodontics and Dentofacial Orthopedics.  
Fellow- World Federation of Orthodontist, USA. |
<p>| Santhosh Kumar              | Reader, Department of Periodontology, Manipal University, Manipal |
| Gaurav Singhal              | Master of Tropical Veterinary Sciences, currently pursuing Ph.D in Medicine |
| Dr. Aarti Garg              | Bachelor of Dental Surgery (B.D.S.) M.D.S. in Pedodontics and Preventive Dentistry Pursuing Phd in Dentistry |</p>
<table>
<thead>
<tr>
<th>Name</th>
<th>Qualifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sabreena Safuan</td>
<td>Ph.D (Pathology) MSc (Molecular Pathology and Toxicology) BSc (Biomedicine)</td>
</tr>
<tr>
<td>Arundhati Biswas</td>
<td>MBBS, MS (General Surgery), FCPS, MCh, DNB (Neurosurgery)</td>
</tr>
<tr>
<td>Getahun Asebe</td>
<td>Veterinary medicine, Infectious diseases, Veterinary Public health, Animal Science</td>
</tr>
<tr>
<td>Rui Pedro Pereira de Almeida</td>
<td>Ph.D Student in Health Sciences program, MSc in Quality Management in Healthcare Facilities</td>
</tr>
<tr>
<td>Dr. Suraj Agarwal</td>
<td>Bachelor of dental Surgery Master of dental Surgery in Oromaxillofacial Radiology. Diploma in Forensic Science &amp; Odonontology</td>
</tr>
<tr>
<td>Dr. Sunanda Sharma</td>
<td>B.V.Sc.&amp; AH, M.V.Sc (Animal Reproduction, Obstetrics &amp; gynaecology), Ph.D.(Animal Reproduction, Obstetrics &amp; gynaecology)</td>
</tr>
<tr>
<td>Osama Alali</td>
<td>PhD in Orthodontics, Department of Orthodontics, School of Dentistry, University of Damascus, Damascus, Syria. 2013 Masters Degree in Orthodontics.</td>
</tr>
<tr>
<td>Shahanawaz SD</td>
<td>Master of Physiotherapy in Neurology PhD- Pursuing in Neuro Physiotherapy Master of Physiotherapy in Hospital Management</td>
</tr>
<tr>
<td>Dr. Prabudh Goel</td>
<td>MCh (Pediatric Surgery, Gold Medalist), FISPU, FICS-IS</td>
</tr>
<tr>
<td>Dr. Shabana Naz Shah</td>
<td>PhD in Pharmaceutical Chemistry</td>
</tr>
<tr>
<td>Rauof Hajji</td>
<td>MD, Specialty Assistant Professor in Internal Medicine</td>
</tr>
<tr>
<td>Vaishnavi V.K Vedam</td>
<td>Master of dental surgery oral pathology</td>
</tr>
<tr>
<td>Surekha Damineni</td>
<td>Ph.D with Post Doctoral in Cancer Genetics</td>
</tr>
<tr>
<td>Tariq Aziz</td>
<td>PhD Biotechnology in Progress</td>
</tr>
</tbody>
</table>
CONTENTS OF THE ISSUE

i. Copyright Notice
ii. Editorial Board Members
iii. Chief Author and Dean
iv. Contents of the Issue

1. Retroperitoneal Liposarcoma: A Case Report and Review of Literature. 1-7
2. Comparison of Cervical and Vaginal Specimens for HPV/DNA Test for Screening Cervical Carcinoma among 35 Year Age Cohort Ever Married Women in a District of Sri Lanka: A Cross Sectional Study. 9-14
3. A Conceptual Study of Drishti in Ayurvedic and Modern Point of View. 15-21
4. Ceftriaxone-Induced Gallbladder Stones in Children. 23-27
5. Survival Analysis for Pancreatic Cancer Patients using Cox-Proportional Hazard (CPH) Model. 29-46

v. Fellows
vi. Auxiliary Memberships
vii. Preferred Author Guidelines
viii. Index
Introduction- Liposarcomas are rare malignant tumours of adipocytic differentiation and are classified under the soft tissue sarcoma subtype histologically. Retroperitoneal liposarcoma (RPL) has an incidence of 1 per 2.5 million individuals, and the retroperitoneum is the second most common site for a liposarcoma, following the lower limb as the most common site. The retroperitoneum is a space that can easily expand; therefore, tumours grow in this space without any symptoms until they are very large.

This case study reports a patient diagnosed with a retroperitoneal liposarcoma treated with primary radical surgery and the patient is currently being followed-up in our unit with close monitoring and Computed Tomographic (CT) imaging. The patient consented to the reporting of this case.

GJMR-F Classification: NLMC Code: WJ 768
I. INTRODUCTION

liposarcomas are rare malignant tumours of adipocytic differentiation and are classified under the soft tissue sarcoma subtype histologically. Retroperitoneal liposarcoma (RPL) has an incidence of 1 per 2.5 million individuals, and the retroperitoneum is the second most common site for a liposarcoma, following the lower limb as the most common site. The retroperitoneum is a space that can easily expand; therefore tumours grow in this space without any symptoms until they are very large.

This case study reports a patient diagnosed with a retroperitoneal liposarcoma treated with primary radical surgery and the patient is currently being followed-up in our unit with close monitoring and Computed Tomographic (CT) imaging. The patient consented to the reporting of this case.

II. CASE REPORT

A 70-year-old female patient was referred to our unit for assessment of an asymptomatic solid left sided adnexal mass seen on CT scan during evaluation for aurological complaint.

At the time of the referral the mass measured 5.5 x 4.9 x .7.2 cm with a macroscopic fat and a large soft tissue component on CT-scan assessment. Tumour markers were all essentially normal, CA 125 of 15 U/mL, CA 19.9 of U/mL, CEA of 2.8 ug/L and the AFP 13.4 k/U, which is a slightly raised level. During this assessment, an excisional procedure was offered to the patient, but due to the Covid 19 pandemic the patient opted to wait with a surgical procedure and follow-up at a later stage.

The patient presented 9 months later for re-assessment. During this time the mass had increased significantly in size and had become symptomatic and palpable in the left lower quadrant of her abdomen. On repeat CT-scan the mass appeared to have significantly increased in size, measuring 12x 8 x 14 cm. The mass still had a predominantly solid appearance and was strongly associated to the left ovary and likely ovarian in origin. Ovarian cancer markers were repeated and as above stayed within normal limits. Due to the appearance of the lesion and the very rapid growth, a non-benign lesion, possibly of ovarian origin was suspected and an explorative/staging laparotomy was offered to the patient. The patient consented to the procedure. A mid-line laparotomy was performed, and a large retroperitoneal mass was found. This mass was adherent to the left ovary, left ureter, left psoas muscle and external iliac vessels as well as the sigmoid colon. With careful anatomical dissection the mass was resected, and a full staging laparotomy and lymph node sampling of the left pelvic and para-aortic lymphnodes was performed. The specimen comprised of a 527g encapsulated, lobulated portion of tissue, with a histological diagnosis of a well differentiated liposarcoma, sclerosing variant. No areas of dedifferentiated liposarcoma were noted and the margins were clear of tumour. All resected lymph nodes were negative for metastatic disease. The patient had an uneventful post-operative recovery.

Although the retroperitoneal liposarcoma appears to have been removed completely in this patient, local recurrence is likely. Since there is currently no evidence that radiotherapy or chemotherapy improves survival rates or recurrence rates of the disease in the immediate adjuvant setting, the patient did not receive any adjuvant therapy and is being monitored closely with clinical examinations and 3 monthly CT-scans to evaluate for any local or distant recurrent disease.

III. DISCUSSION

a) Surgical and Anatomical features

The retroperitoneum and the pre-peritoneum forms the extraperitoneal space, which is the portion of the pelvis and abdomen which does not lie within the peritoneal space. The retroperitoneal space is an almost virtual and expandable space, defined anteriorly by the peritoneal extensions anchoring the transverse colon, the small bowel as well as the ascending and descending colon, part of the duodenum, part of the pancreas and part of the liver. The retroperitoneum contains the kidneys, the adrenal glands, the pancreas, part of the duodenum, ascending and descending colon, the abdominal aorta and vena cava (dividing into the common iliac, external and internal iliac arteries and veins respectively), the abdominal lymphnodes groups and tracts, six major nerves and the autonomic lumbar nerve chains and the connective tissue of fasciae, with the White line of Toldt as the fusion between the mesocolon and the posterior retroperitoneum.

Author: Life the Glynnwood Hospital, Benoni, South Africa.
e-mail: elize.wethmar@gmail.com
Treatment of most conditions involving the retroperitoneum requires surgical intervention. A complete and thorough understanding of the anatomy of the structures involving the retroperitoneum is prudent in avoiding inadvertent damage to underlying structures. Complications may arise from inadvertent damage to structures located within the retroperitoneum during surgical manipulation or instrumentation.

**Histopathological features**

Retroperitoneal liposarcomas usually consist of a large, well-circumscribed, lobulated mass. Variable consistencies are present, from yellow to firm grey to gelatinous areas, depending on the proportion of fat, fibrous and myxoid components. Larger retroperitoneal tumours appear more heterogeneous, often containing foci of fat necrosis and punctate haemorrhages.

![Figure 1: Macroscopic appearance of the excised retroperitoneal liposarcoma](image)

As in many tumours, the histological classification of liposarcoma has evolved over the past several decades, mostly owing to the advances in our understanding of molecular genetics.

The most recent World Health Organisation (WHO) classification system (2020) recognized five different types of major liposarcoma subtypes, differentiated by distinctive morphologies and unique genetic findings:

- Atypical lipomatous tumour (ALT)/ well differentiated liposarcoma (includes adipocytic [or lipoma like], sclerosing and inflammatory variants)
- Dedifferentiated liposarcoma
- Myxoid liposarcoma
- Pleomorphic liposarcoma
- Myxoid pleomorphic liposarcoma

In atypical lipomatous tumour/well differentiated liposarcoma adipocytic variant consists out of cells that vary substantially in size as well as cells that have nuclear atypia in fat or spindle cells. Lipoblasts can be present in various numbers, but the presence or absence is not necessary for the diagnosis of a liposarcoma. Sclerosing atypical lipomatous tumour presents second most frequently and is most often seen in the retroperitoneum or spermatic cord. The most important histological finding is scattered bizarre stromal cells, showing marked nuclear hyperchromasia. Inflammatory ALT represents the rarest subtype, occurring most often in the retroperitoneum.
Figure 2: Low power microscopy view demonstrating a deifferentiated liposarcoma

Figure 3: A microscopic view of a lipoblast, which may or may not be present in a liposarcoma
Dedifferentiated liposarcoma can arise as a synchronous lesion in 90% of cases and as metachronous lesion in 10% of cases. These tumours exhibit a wide morphological spectrum and histologically show areas of high grade, poorly differentiated sarcoma resembling high-grade myxofibrosarcoma, fibrosarcoma, malignant solitary fibrous tumour or pleomorphic sarcoma not otherwise specified. Dedifferentiated liposarcomas can be of variable histological grade. Dedifferentiated liposarcomas is an aggressive disease, arising most commonly in the retroperitoneum and is associated with high rates of local and metastatic recurrence and disease specific mortality.

Use of the term atypical lipomatous tumour is determined by tumour location and resectability. In locations such as the retroperitoneum, it is usually impossible to obtain a wide tumour free surgical margin of more than 2cm, thus local recurrence is common and leads to mortality, seen in the absence of dedifferentiation or metastases.

c) Radiological features

The introduction of computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography have greatly enhanced our capability to make the diagnosis of abdominopelvic neoplasms and determine and direct treatment, as well as observe the progress of the neoplasm and effect of treatment over time. Identification of a retroperitoneal mass at imaging is a challenging task for radiologists, however the presence of fat within a retroperitoneal lesion is helpful in refining the differential diagnosis. It is easy to recognize fat within a lesion due to its characteristic imaging appearance:

- On ultrasound appearance it is hyperechoic and may demonstrate posterior acoustic shadowing
- Computed Tomographic (CT) imaging derives contrast parameters predominantly from the physical properties of tissue – in combination with high resolution spiral CT, this provides accurate attenuation measurement, with –10 to -100 HU corresponding to fat
- Magnetic resonance imaging (MRI) has lower spatial resolution than CT imaging, but better soft tissue contrast and greater sensitivity in detection of microscopic fat. The two MRI techniques for the identification of fat within a structure are fat saturation and chemical shift imaging

It can be difficult to localize large abdominal masses to an anatomical space and to accurately identify the organ of origin thus to determine whether the lesion arises from a retroperitoneal organ, or from the soft tissue. If the mass is surrounded by the parenchyma of the organ, it undoubtedly arises from the organ, however if the mass originates at the margin of the organ, it is more difficult the determine the origin. The interface between the mass with the adjacent organ can provide insight as to whether it displaces the organ or arises from the organ (Table 1).
**Table 1:** Positive signs indicating that a Retroperitoneal Tumour Arises from an Adjacent Organ

<table>
<thead>
<tr>
<th>Sign</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beak sign</td>
<td>Sharp beak shape of organ of origin occurs at the edge of the interface with the tumour</td>
</tr>
<tr>
<td>Embedded organ Sign</td>
<td>Organ of origin is encased by the tumour, without a sclerotic interface</td>
</tr>
<tr>
<td>Phantom (invisible) organ sign</td>
<td>Organ of origin is obliterated by the tumour</td>
</tr>
<tr>
<td>Prominent feeding artery sign</td>
<td>Large feeding arteries of a hypervascular tumour point to the organ of origin</td>
</tr>
</tbody>
</table>

A CT image of a lipoma will reveal a well-defined homogenous mass with fat attenuation. Areas of soft-tissue attenuation may be seen within the tumour and may represent fat necrosis, septa or normal adjacent structures. If a predominantly solid soft-tissue component or adjacent organ invasion is present, a liposarcoma should be suspected. The imaging characteristics of liposarcomas differs, depending on the histological subtype. Well-differentiated liposarcomas appear as well defined predominantly fat-containing lesions with minimal soft tissue attenuation and commonly contain septa – the appearance may be indistinguishable from a lipoma and therefore a retroperitoneal purely fatty lesion should be considered a liposarcoma rather than a lipoma until proven otherwise with histological confirmation. Dedifferentiated liposarcomas appear remarkably similar to well-differentiated liposarcomas of CT imaging, and dedifferentiation is suggested by focal nodular non-lipomatous regions larger than 1 cm.

*Figure 5:* Transverse CT-scan image demonstrating a liposarcoma
d) Treatment options

i. Surgery

Surgery is the mainstay of treatment for non-metastatic retroperitoneal sarcoma. If possible, macroscopically complete resection of tumour should be aimed for and this can lead to radical surgery requiring en-bloc removal of adjacent structures. If the pre-treatment diagnosis can be made with certainty, based on radiologic and clinical findings and complete resection is deemed possible, pre-treatment biopsy is not advised and has no value. If radiologic investigations suggest a pathology that does not require primary surgery (e.g. lymphoma, Ewing Sarcoma, GIST) or the incomplete resection is expected, biopsy will be necessary to plan alternative treatment. Image guided core biopsy is advised and preferred over open or laparoscopic approaches, which may be associated with tumour spillage and compromise future surgical strategy by altering tissue planes.

The removal of the entire tumour with a margin of normal tissue is usually not possible in large retroperitoneal liposarcomas due to the presence of adjacent large vessels, nerves and bony structures, leading to local recurrence in the abdomen, which constitutes the cause of death in three out of four patients. High grade, dedifferentiated tumours are at a higher risk to recur and spread systemically, so even if extensive surgery with adequate margins is achieved, the prognosis remains dismal, querying the fact whether a patient should be exposed to the morbidity of extensive surgery if the mortality in dedifferentiated liposarcoma remains high irrespective of treatment.

ii. Radiation Therapy

Currently there is no convincing evidence for the role of radiotherapy (RT) in the adjuvant setting for the management of RLS. Several authors have analysed the data from the surveillance, epidemiology, and end result (SEER) data base in order to define the role of adjuvant RT in RLS and as a general finding it did not improve survival or did so in a subgroup of patients with stage I disease only. To date, no randomised trials have been completed or published comparing surgery alone with combined surgery and RT. Pre-operative RT in certain settings is showing some promise, however further studies and data would be needed.
Systemic therapy
Chemotherapy has an established role in the palliative management of advanced or metastatic soft tissue sarcoma. Active agents include the anthracyclines (doxorubicin and epirubicin) and the alkylating agent ifosfamide\(^1\). In patients with resistant disease, gemcitabine, docetaxel, trabectedin and pazopanib were established as effective second- or third-line options in the recent years\(^17\).

The response of liposarcoma to chemotherapy differs according to histological subtype and grade\(^6\). Well-differentiated and dedifferentiated liposarcoma respond poorly to systemic therapy, therefore novel molecular targets will have to be identified to explore new possibilities for treatment. MDM2 and CDK4 targeted therapy as well as the tyrosine kinase inhibitor Sunitinib is currently showing promise in treatment of RLS\(^8\).

IV. Conclusion
Retroperitoneal liposarcoma is a rare malignancy and challenging to diagnose, treat and monitor for recurrence. The presence of a high-grade dedifferentiated component does make the disease more aggressive, but even well differentiated tumours can be difficult to manage and recurrences can be widespread and higher grade than the primary tumour.

Even though the mainstay of treatment is surgery, multi-disciplinary discussion is paramount, especially in view of anatomically irresectable sights and potential future benefits of non-surgical therapies. As with any rare malignancy national and international collaboration is encouraged to learn from each other and improve management of retroperitoneal liposarcoma.

References Références Referencias

Comparison of Cervical and Vaginal Specimens for HPV/DNA Test for Screening Cervical Carcinoma among 35 Year Age Cohort Ever Married Women in a District of Sri Lanka: A Cross Sectional Study

By Perera, KCM, Mapitigama, N & Abeysena, HTCS

Abstract- Background: Currently, pap smears are used to screen cervical cancers in Sri Lanka. Two major drawbacks of pap smear screening method are the suboptimal sensitivity and the low coverage. HPV/DNA screening method can be used as a cervical cancer screening method and high sensitivity (92.9%) is the major advantage of it. Specimens can be collected for HPV/DNA test from two sampling site a) from the cervix b) from the vagina. Vaginal specimen collection is more feasible as it does not require speculum examination, therefore primary healthcare worker can be collected a specimen. The objective of the study is to compare HPV/DNA test results of specimens from two sampling sites as a measure to improve the quality and coverage of the National Cervical Cancer Screening programme in Sri Lanka.

Keywords: cervical cancer screening, HPV/DNA test, cervical specimens, vaginal specimens, coverage.

GJMR-F Classification: NLMC Code: WP 460

Strictly as per the compliance and regulations of:

© 2021. Perera, KCM, Mapitigama, N & Abeysena, HTCS. This is a research/review paper, distributed under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License http://creativecommons.org/licenses/by-nc/3.0/), permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.
Comparison of Cervical and Vaginal Specimens for HPV/DNA Test for Screening Cervical Carcinoma among 35 Year Age Cohort Ever Married Women in a District of Sri Lanka: A Cross Sectional Study

Perera, KCM, Mapitigama, N & Abeysena, HTCS

Abstract- Background: Currently, pap smears are used to screen cervical cancers in Sri Lanka. Two major drawbacks of pap smear screening method are the suboptimal sensitivity and the low coverage. HPV/DNA screening method can be used as a cervical cancer screening method and high sensitivity (92.9%) is the major advantage of it. Specimens can be collected for HPV/DNA test from two sampling site a) from the cervix b) from the vagina. Vaginal specimen collection is more feasible as it does not require speculum examination, therefore primary healthcare worker can be collected a specimen. The objective of the study is to compare HPV/DNA test results of specimens from two sampling sites as a measure to improve the quality and coverage of the National Cervical Cancer Screening programme in Sri Lanka.

Method: A descriptive cross-sectional study was conducted among 35 year old ever married women in a district of Sri Lanka. Total number of 682 women were recruited randomly from the field. Total number of 621 women were first subjected to vaginal HPV/DNA specimen collection by primary healthcare workers followed by cervical HPV/DNA specimen collection by Medical officers (MOO) or Public Health Nursing Sisters (PHNSS). Specimen screening was carried out at a laboratory using Polymerase Chain Reaction (PCR) technique by cobas 4800 HPV/DNA screening machine. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the vaginal specimens against cervical specimens were computed with their 95% confidence intervals (CI).

Results: The sensitivity, specificity, PPV and NPV of the vaginal HPV/DNA specimen were 100% (95%CI; 90.7%-100%), 98.9% (95% CI; 97.8%-99.6%), 86.4% (95% CI; 74.1%-93.3%) and 100% respectively. Kappa coefficient between vaginal vs cervical HPV/DNA specimen screening method was 0.92 (95%CI: 0.86%-0.98%).

Conclusions: There is a good concordance between cervical vs vaginal HPV/DNA specimen screening method. Vaginal specimen collection method can be used to improve the detection of cervical lesions.

Keywords: cervical cancer screening, HPV/DNA test, cervical specimens, vaginal specimens, coverage.

I. Introduction

Cervical cancer is the 2nd leading cause of female cancer in Sri Lanka (1). Hence in 1998, Sri Lanka took an initiative to include screening for cervical cancer with conventional papanicolaou (pap) smear in the Well Woman Clinics (WWCs) (2). However, even after 20 years of cervical cancer screening (with pap smears), there is no marked reduction in incidence, morbidity and mortality of cervical cancer in Sri Lanka. Two major drawbacks of the present programme are, the suboptimal sensitivity of the pap smear (53%) (3) to detect Cervical Intraepithelial Neoplasia (CIN) II and the low coverage of the cervical cancer screening programme.

Cervical cancers are virtually associated with human papillomavirus (HPV) infection. HPV/DNA screening test screens for high risk carcinogenic HPV antigens. Cobas 4800 HPV/DNA screening test detects fourteen high risk cervico-vaginal carcinogenic HPV genotypes such as; 16, 18 and 12 pooled high risk (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) (4). There are two methods of specimen collection for HPV/DNA screening test such as; vaginal and cervical. The sensitivity of cobas 4800 HPV/DNA screening test for cervical specimen to detect CIN II (92.9%) (4) is high, therefore the detection rate of cervical lesions are very high.

The major problem lies behind the lower coverage of pap smear screening programme in a country is the requirement of a vaginal speculum examination by field public health Medical Officers called Medical Officers of Health (MOOH), Medical Officers attached to health care institutions or Public Health Nursing Sisters (PHNSS) as well as qualified staff categories for cyto-screening (Consultant Histopathologists and cytoscreeners). Non-cytological
screening method, which doesn’t requires vaginal speculum examination (i.e. HPV/DNA vaginal specimen) may improve the coverage of National Cervical Cancer Screening Programme in Sri Lanka. The objective of the study is to compare HPV/DNA test results of specimens from two sampling sites a) from the cervix and b) from the vagina among 35 year age cohort ever married women in Kalutara district as a measure to improve the quality and coverage of the National Cervical Cancer Screening programme in Sri Lanka.

II. Methods

A descriptive cross-sectional study was conducted in public health administrative areas called MOH areas of Kalutara district since September/2018 to January/2019 to compare screening results between cervical and vaginal methods of HPV/DNA specimen collection. The study population comprised of ever married women in 35 year of age in Kalutara district. Women with diagnosed invasive cervical cancer, women with vaginal bleeding and active infection at the time of examination with evidence of medical records or by visual inspection, women currently on treatment for HPV infection, pregnant women and women ≤ 3 months in the post partum period, women who had undergone hysterectomy, women with diagnosed physical or mental retardation or disease status and women who are not resident within the district continuously for ≥ three months prior to the date of the survey were excluded from the study.

Sample size calculation for diagnostic test accuracy was done (5). Sensitivity of vaginal specimen vs cervical specimen for CIN II or worse in Polymerase Chain Reaction (PCR) based screening method was 99% (6). Prevalence (P) of the disease in the target population was 3.3% (7). In a case of preliminary studies, if there is a resource limitation setting, investigators may use a lower precision of >10% (8), (9). Therefore, we needed 386 women. Further adjustment to the sample size was made by considering the previous year WWC non-response rate (42.4%) in Kalutara district (10) and the final required sample size was 671.

A MOH area is divided in to several Public Health Midwife (PHM) areas. Total number of PHM areas in Kalutara district was 413. Public Health Midwife area eligible families register/s was/were the sampling frame. Two women from each PHM area eligible families register/s were randomly selected to the study. Total number of 682 ever married women of 35 year old aged were recruited to the study after applying exclusion criteria at field setting and invited to field WWCs in Kalutara district (89). Age was calculated using the date of birth by recall or by using an National Identity Card and was approximated to the last completed year.

Staff trainings for PHMM to collect upper vaginal HPV/DNA specimen and MOOH or Public Health Nursing Sisters (PHNSS) to collect cervical HPV/DNA specimen was done by the first author at each MOH office level in Kalutara district. Fifteen such staff trainings were conducted on monthly PHMM in-service training day at each MOH office. Videos created for staff trainings by the cobas 4800 HPV/DNA screening machine manufactures (Hologic company for women’s health) was used in staff trainings. Instruction regarding accurate numbering of specimens, completion of specimen request forms and preparation for transport were also included in the training sessions. Cytoscreeners were uniformly trained for specimen barcoding, handling the machine and report writing to ensure the quality of performance by team of experts. Colposcopists were uniformly trained to ensure the quality of performance.

Information regarding socio-demographic characteristics were gathered by using an interviewer administered questionnaire. First HPV/DNA vaginal specimen collection was carried out by well-trained PHM and then cervical specimen collection from the same client by MOH/PHNS at the same clinic session in a separate place. Cusco’s speculum was inserted to visualize cervix before obtaining HPV/DNA cervical specimen. HPV/DNA specimen obtained from the cervix and vagina using a special broom-like devices were separately placed into HPV/DNA specimen collection containers. Cervical and vaginal specimen from the same client were separately packed with the same identification number. In vaginal specimens, the letter “V” was written after the identification number for identification purpose.

Prepared guidelines were strictly adhered during data collection, barcoding and preparation for transport. Monitoring and supervision of the ongoing field activities and specimen collection were carried out by the first author. Specimen identification numbers were closely supervised by the first author at community clinic level for vaginal and cervical specimens including in request forms. Barcoding of specimens at the laboratory before entering to the cobas 4800 machine were done under first author’s close monitoring and supervision. Result report writing by cyto-screeners at the laboratory were randomly checked.

Cervical specimens were screened at the laboratory by well trained cyto-screeners with cobas 4800 HPV/DNA automated PCR machine, which consists of cobas 4800x instrument and cobas analyzer. Cobas 4800 HPV/DNA screening machine was included several quality control mechanisms such as internal quality control, external quality control and contamination control.

The test sensitivity and specificity to detect ≥ CIN II is 92.9% and 71% respectively (4). It detects 14 high risk carcinogenic HPV genotypes, such as; 16,18
and 12 pooled high risk (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68).

Data were analysed by using SPSS version 20. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of vaginal specimen vs cervical specimen (gold standard) and 95% Confidence Intervals (CI) were calculated. Overall cervico-vaginal HPV infection and subgroup analysis (genotype 16 & 18) by cervical and vaginal specimen and 95% CI were calculated.

III. RESULTS

Six hundred eighty two women were recruited to the study and only 631 of them were attended to community WWCs, therefore the response rate was 92.5%. Of them only 621 were subjected to vaginal and cervical specimen collection after applying exclusion criteria at clinic setting.

One recruit was excluded at the clinic setting from the study, as she was pregnant (n=1), while others were excluded due to cervical erosion (n=3), vaginal discharge (n=3), cervicitis (n=2) and fungal infection (1).

Majority of respondents were Sinhala (94.5%) and Buddhist (94.4%). Out of the total subjects 9% had not completed years of school education beyond the 5th grade and another 12.9% of the subjects were remained at 6-11th grade of level education. Majority were educated only up to O/L passed level of education (58.9%). (Table 1)

Table 1: Distribution of participants according to ethnicity, religion, educational level and occupational status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of women (n)</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nationality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinhala</td>
<td>587</td>
<td>94.5</td>
</tr>
<tr>
<td>Tamil</td>
<td>13</td>
<td>2.1</td>
</tr>
<tr>
<td>Muslim</td>
<td>21</td>
<td>3.4</td>
</tr>
<tr>
<td>2. Religion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buddhism</td>
<td>586</td>
<td>94.4</td>
</tr>
<tr>
<td>Catholic</td>
<td>3</td>
<td>0.4</td>
</tr>
<tr>
<td>Hindu</td>
<td>11</td>
<td>1.8</td>
</tr>
<tr>
<td>Islam</td>
<td>21</td>
<td>3.4</td>
</tr>
<tr>
<td>3. Education level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No schooling</td>
<td>2</td>
<td>0.3</td>
</tr>
<tr>
<td>Grade 1-5th</td>
<td>54</td>
<td>8.7</td>
</tr>
<tr>
<td>Grade 6-11th</td>
<td>80</td>
<td>12.9</td>
</tr>
<tr>
<td>O/L passed</td>
<td>230</td>
<td>37.0</td>
</tr>
<tr>
<td>A/L passed</td>
<td>164</td>
<td>26.4</td>
</tr>
<tr>
<td>Degree &amp; above</td>
<td>91</td>
<td>14.7</td>
</tr>
<tr>
<td>4. Occupational status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working women</td>
<td>184</td>
<td>29.6</td>
</tr>
<tr>
<td>Non-working women</td>
<td>437</td>
<td>70.4</td>
</tr>
<tr>
<td>Total</td>
<td>621</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Sensitivity, specificity, PPV and NPV of the vaginal vs cervical HPV/DNA specimen collection screening method were 100% (95% CI: 90.7%-100%), 98.9% (95% CI: 97.8%-99.6%), 86.4% (95% CI: 74.1%-93.3%) and 100% (95% CI: 90.7%-100%) respectively (Table 2).

Table 2: HPV/DNA vaginal specimen collection screening method vs cervical HPV/DNA specimen collection screening method (as a gold standard) by using cobas 4800 HPV/DNA screening test

<table>
<thead>
<tr>
<th>Screening test +ve/-ve</th>
<th>Cervical HPV/DNA specimen +ve for HR-HPV</th>
<th>Cervical HPV/DNA specimen -ve for HR-HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal HPV/DNA* specimen +ve for HPV</td>
<td>38</td>
<td>06</td>
</tr>
<tr>
<td>Vaginal HPV/DNA specimen -ve for HPV</td>
<td>0</td>
<td>577</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>583</td>
</tr>
</tbody>
</table>

*HPV/DNA: Human papillomavirus/DNA
Diagnostic agreement between vaginal vs cervical HPV/DNA specimen collection screening method was 99.0% (95% CI: 97.9%-99.6%). Positive Likelihood Ratio (LR +), Negative likelihood ratio (LR -) for vaginal specimen screening were 97.2 (95% CI: 43.8-215.4), and 0.0 respectively. Kappa coefficient between vaginal vs cervical HPV/DNA specimen screening method by cobas 4800 HPV/DNA test was 0.92(95% CI; 0.86-0.98).

Prevalence of cervico-vaginal HPV infection among 35 year age cohort ever married women in Kalutara district, according to the cervical specimen screening method by cobas 4800 was 6.12% (95% CI; 4.26%-8.3%), while the percentage of HPV infection positives among 35 year age cohort ever married women in Kalutara district according to the vaginal specimen screening method by cobas 4800 test was 7.08% (95% CI; 5.2%-9.4%).

Prevalence of HR-HPV 16 & 18 genotype infection among 35 year age cohort ever married women in Kalutara district according to the vaginal specimen collection screening method was 2.1% (95% CI; 2.09%-2.11% (Table 4).

**Table 3:** Distribution of participants according to cervical HPV/DNA specimen screening result for HR-HPV genotypes

<table>
<thead>
<tr>
<th>Cervical HPV/DNA specimen results for HR-HPV genotype</th>
<th>Number of women</th>
<th>Percentage %</th>
<th>95% CI for percentages %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>583</td>
<td>93.9</td>
<td></td>
</tr>
<tr>
<td>12 pooled positive</td>
<td>26</td>
<td>4.2</td>
<td>4.18-4.22</td>
</tr>
<tr>
<td>16positive</td>
<td>10</td>
<td>1.6</td>
<td>1.59-1.61</td>
</tr>
<tr>
<td>18positive</td>
<td>02</td>
<td>0.3</td>
<td>0.29-0.31</td>
</tr>
<tr>
<td>Total</td>
<td>621</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4:** Distribution of participants according to vaginal specimen screening result for HR-HPV genotypes

<table>
<thead>
<tr>
<th>Vaginal HPV/DNA specimen results for HR-HPV genotypes</th>
<th>Number of women</th>
<th>Percentage %</th>
<th>95% CI for percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>577</td>
<td>92.92</td>
<td>92.88-92.92</td>
</tr>
<tr>
<td>12 pooled positive</td>
<td>31</td>
<td>5.0</td>
<td>5.28-5.32</td>
</tr>
<tr>
<td>16positive</td>
<td>11</td>
<td>1.78</td>
<td>1.79-1.81</td>
</tr>
<tr>
<td>18positive</td>
<td>02</td>
<td>0.3</td>
<td>0.29-0.31</td>
</tr>
<tr>
<td>Total</td>
<td>621</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

**IV. DISCUSSION**

According to 2012 estimates, annually 1721 new cervical cancer cases are diagnosed in Sri Lanka and 690 are died due to the disease (1). Total number of 111,798 of 35 year age cohort ever married population were screened under the National Cervical Cancer Screening programme in 2016 and the coverage was 52.8% (10). Cervical smears reported as malignant were 44 (0.03%) and cervical smears reported as high and low grade lesions were 665 (0.5%), which shows the underreporting due to low coverage of the programme.

Sensitivity, specificity, positive predictive value and negative predictive value of the vaginal HPV/DNA specimen screening vs cervical HPV/DNA specimen screening were 100%, 98.9%, 86.4% and 100% respectively, while the false positive rate was high in vaginal HPV/DNA specimen screening (1.1%).

As a screening method most précised value of the vaginal HPV/DNA specimen screening was zero reporting of the false negatives vs gold standard screening which would not let missing and under reporting cases. Similar pattern of results were observed in the world by using different PCR tests in comparison studies of vaginal HPV/DNA specimen screening vs cervical HPV/DNA specimen screening (6, 10, 11).

Prevalence of overall cervico-vaginal HPV infection among 35 years old ever married women was 6.12%, while the percentage of cervico-vaginal infection by vaginal HPV/DNA specimen screening method was 7.08%. Prevalence of HPV infection by genotypes 16 & 18 was 1.9%, while the percentage of cervico-vaginal infection positive by vaginal HPV/DNA specimen screening method was 2.1%.

Slight over reporting rate of vaginal HPV/DNA specimen screening method was observed due to the lower specificity rate, which might lead to over treatment and unnecessary anxiety due to the fear of disease.

Agreement between the vaginal HPV/DNA specimen screening method vs cervical HPV/DNA screening was 0.99, while the kappa coefficient between the two test was 0.92. Similar agreement was shown in the world by using different PCR tests in comparison studies of vaginal HPV/DNA specimen screening vs cervical HPV/DNA specimen screening (5, 10, 12).

Specimens were transferred to the laboratory in a special regiform box with a cool pack to maintain the temperature regime (2c°-30c°), while during the
transport. Vaginal HPV/DNA specimen can be obtained with a cotton swab combined with glass slide and successfully attempted in some other countries (13), which can be a suitable measure to overcome the associated challenge with specimen storage and transportation in “thinprep cell collection media”.

The major advantage of the vaginal HPV/DNA specimen collection was it doesn’t require speculum examination and PHMM can be collected specimens. Therefore, vaginal specimen collection method can be used to improve the quality and coverage of the National Cervical Cancer Screening programme in Sri Lanka. This study was restricted to one district out of 25 districts in Sri Lanka due to logistic constrains. Population characteristics and the public health infrastructure of the district favored generalizability of the research findings to the whole country.

V. Conclusion

The concordance between cervical vs vaginal specimen screening method by cobas 4800 PCR based HPV/DNA screening test was very high. Vaginal specimen collection method is more feasible and can be used to improve the detection of cervical lesions, therefore improve the quality and coverage of the National Cervical Cancer Screening programme.

Abbreviations
WWC: Well Woman Clinic,
CI: Confidence Interval,
MOOH: Medical Officers of Health,
PHNSS: Public Health Nursing Sisters,
PHMM: Public Health Midwives,
PCR: Polymerase Chain Reaction
PPV: Positive Predictive value
NPV: Negative Predictive Value

Ethical approval and consent to participate
Ethical clearance was obtained from the Ethics Review Committee (ERC), National Institute of Health Science, Kalutara. Informed written consent was obtained from each of the selected participants at the field during the study. Confidentiality was highly maintained, While handing over individual HPV/DNA result reports. Administrative clearance to conduct the study was obtained from Provincial Director of Health Services Western Province, Regional Director of Health Services Kalutara district, Director District General Hospital Kalutara and Director National Institute of Health Science Kalutara.

Consent for publication
Not applicable

Availability of data and materials
The datasets used to analyse in this study is available at corresponding author on reasonable request.

Competing interests
Authors were declared that they have no competing interests.

Funding
We hereby declare that the cost for specimen collection instruments and reagents (test kits) was funded by Family Health Bureau, Colombo, Sri Lanka. There was no any influence from the above mentioned institute during the process of conducting or report writing of this research.

Authors contribution
KCMP was participated in the design of the study, coordinated data collection performed the statistical analysis and drafted the version of the manuscript. HTCSA was performed the statistical analysis and interpreted data. Both HTCSA and NM were helped to draft the manuscript. All three authors were read and approved the final manuscript.

Acknowledgement
We are grateful to the study participants, research assistants and the Post Graduate Institute of Medicine, University of Colombo.

References Références Referencias


A Conceptual Study of Drishti in Ayurvedic and Modern Point of View

By Dr. Kavita Rathore, Dr. Manish Choudhari & Dr. Naresh Jain

Abstract- There are five sense organs (Panch Gyanendriya) mentioned in Ayurvedic Samhitas i.e. eye(chakshu), ear(shrota), nose(ghrana), tongue(rasana) and skin(twak). One of these is eye (Drishti) which is most important sense organ in our body. Acharya Sushruta the eminent Ayurveda region, has described the Drishti very accurately in his treatise Sushruta Samhita. There are six Netra Patala told in Ayurvedic classics which can be anatomically correlated with different layers of eyes as explained in modern ophthalmology. Drishti is a controversial word in Shalakya Tantra, a lot of meanings of Drishti have been taken in the Sushruta Samhita. So Drishti can be simply considered as the functional unit of eye, which performs vision. It is not mere an anatomical structure but the composition of all the essential dhatus of internal eye ball. In ancient Ayurvedic scriptures have explained Netra Rachna Sharir and Kriya Sharir in a beautiful descriptive manner, still there is need of exploring the terminologies for proper understanding of pathogenesis of Netra Rogas and their managements so that implementation of Ayurvedic concepts can be done in eradication of Drishtigata Rogas in a fruitful manner to serve the humanity.

Keywords: drishti, sense organ, acharya sushruta.

GJMR-F Classification: NLMC Code: WB 55.A9
A Conceptual Study of Drishti in Ayurvedic and Modern Point of View

Dr. Kavita Rathore °, Dr. Manish Choudhari ° & Dr. Naresh Jain °

Abstract- There are five sense organs (Panch Gyanendriya) mentioned in Ayurvedic Samhitas i.e. eye(chakshu), ear(shrota), nose(ghrana), tongue(rasana) and skin(twak). One of these is eye (Drishti) which is most important sense organ in our body. Acharya Sushruta the eminent Ayurveda region, has described the Drishti very accurately in his treatise Sushruta Samhita. There are six Netra Patala told in Ayurvedic classics which can be anatomically correlated with different layers of eyes as explained in modern ophthalmology. Drishti is a controversial word in Shalakya Tantra, a lot of meanings of Drishti have been taken in the Sushruta Samhita. So Drishti can be simply considered as the functional unit of eye, which performs vision. It is not mere an anatomical structure but the composition of all the essential dhatus of internal eye ball. In ancient Ayurvedic scriptures have explained Netra Rachna Sharir and Kriya Sharir in a beautiful descriptive manner, still there is need of exploring the terminologies for proper understanding of pathogenesis of Netra Rogas and their managements so that implementation of Ayurvedic concepts can be done in eradication of Drishtigata Rogas in a fruitful manner to serve the humanity.

Keywords: drishti, sense organ, acharya sushruta.

1. Introduction

S halakya Tantra is an important branch in Ashtang Ayurveda which deals with the diseases manifesting above supraclavicular region (Urdhwa jatrugata roga). Netra Sharira deals with three major parts of eye-Mandala, Sandhi and Patala. Amont five Drishti Mandala is one which is situated in the innermost part of eyeball and in context with this all Drishtigata Rogas have been described. Drishti is made up of Panchamahabhuta, but Teja mahabhuta is predominant in the form of Alochaka Pitta. There are two types of Alochaka pitta-1. Chaksu vaisheshika (Dristipatala-image formation occur). 2. Buddhi vaisheshika (Higher visual center-image analysed and perceived by buddhi). Drishti is an important part of eye and in classics it is interpreted in various aspects.

Drishti: The word “drishti” is derived from the “drish” dhatu by adding the “ktin” pratyaya. The meaning of the drishti is process by which we see. Different Acharyas have different view regarding meaning of drishti which are follows.

1. Drishti (Retina)
2. Drishti (Vision)
3. Drishti mandala (Pupil)
4. Drishti mani (Crystalline lens)

Drishti (Retina, Optic nerve)- Some drishtigata rogas like Shleshma vidagdha drishti, Dhun达尔shi, Pitta vidagdha drishti, Nakulandhya, Haswajadya, Gambhirika can only be explained if drishti word is taken as retina or optic nerve.

Drishti (Vision or power to see things)- Acharya Sushruta has explained that Adhimantha destroys the drishti if not treated well in time. From this fact it can be deduced that drishti is the power to see things.

Drishti mandala (Pupil)- Acharya Sushruta has described five Mandala’s in the eye out of which innermost one is Drishti mandala. Drishti Mandala is said to be situated just next to Krishna Mandala. As per modern ophthalmology the eyeball comprises three coats:

Outer (Fibrous coat): anterior 1/6th cornea and posterior 5/6th sclera

Middle (vascular coat): ciliary body, iris, choroid

Inner (nervous coat): retina

Also according to modern ophthalmology as we go anteroposteriorly, the structure next to cornea is pupil.

Pramana of Drishti Mandala: Size of drishti as per Sushruta acharyas is 1/7th of Krishna Mandala. At some places it is written 1/9th of Krishna Mandala. This is in accordance with the fact that pupil is reactive to light and always keep constricting and dilating physiologically. In other words, pupil size is not constant throughout a day. Moreover, drishti is vivarakriti which means like a hole or like a shutter of camera, this supports that drishti is pupil.

Drishti mani (Crystalline lens)- Intraocular crystalline lens placed in posterior chamber of eye ball. As per Sushruta Samhita drishti is masoordal tulya (similar to cotyledons of pulses in shape), which is biconvex in shape. It supports the fact that Drishti is lens as lens is biconvex in shape.

Corresponding Author: P.G. Scholar, Department of Shalakya tantra in National Institute of Ayurveda Jaipur (R.J.)
e-mail: kavitarathore2138@gmail.com
Author: P.G. Scholar, Department of Kayachikitsa in Govt. (Auto.) Dhanwantari Ayurvedic College & Hospital Ujjain (M.P.)
Author: Associate Professor, Department of Kayachikitsa in Govt. (Auto.) Dhanwantari Ayurvedic College & Hospital Ujjain (M.P.)

© 2021 Global Journals
II. Aim and Objective

1. Describing Drishti from an Ayurvedic and Modern point of view.
2. Detailed consideration of all points of Drishti.

III. Materials and Methods

Material- Different Ayurvedic scriptures like Sushruta Samhita, Charak Samhita, Bhela Samhita Modern texts books, Medical journals, Published research paper and Articles.

Method– Study type – Review.

Literature related to the title is searched from all authentic Ayurvedic Scriptures, Ayurvedic journals and internet and Modern texts books.

a) Drishti in Ayurvedic View

Drishti in Anatomical Point of view-

According to Ayurveda the vitiated doshas travel through siras and reach the eye then get localized in the vartmapradesha, sita-asitamandala, sarvakshi or drishti and different diseases of eye are manifested. It is described in Sushruta Samhita that Drishti as a structure itself is covered externally with outer coat (Avrataam bahayen patalen akshi). It has also been told by Acharya Sushruta that while doing Agnikarma (thermal cauterization) on vartma (lids), Drishti should be covered with wet gauze (Drishti achchhadana)14. According to Acharya Charaka also there is indication for Mridusweda (mild fomentation) for Drishti by covering it with padmautpalapatra (leaves of lotus) (Drishti swedayeta mridu naiv va)15. Here Drishti can be considered as an anatomical entity. Appearance of Drishti has been described as glow like a lightening bug or that of minute particle of fire (Khadhyota visfulingabha). Structure of Drishti has been explained as a hole or aperture (Vivarakriti)16.

b) Drishti in Physiological Point of View-

Properties of Drishti-

- Cold atmosphere (Sheet satmya).

Drishti as knowledge-

Drishti visharada is a term used for having extreme knowledgeable person.

Drishti as vision-

In Ayurvedic classics there are several references which indicate that Drishti term is used for vision. Few textual references are as following

- When Tejo Dhatu does not reach Drishti, congenital blindness (Jatyandha) is developed17.
- If poison is given in Anjana form (Visha Samsrishta Anjana) then blurring of vision (Drishti vibhrama) occurs18.

• Controlling vega (natural urges) like Kshudha and Adhovayu leads to defective vision19,20.
• If Adhimantha is not treated properly it leads to loss of vision (Drishtihanana)21.
• Acharya Vaghbhata used term Drishti Mushita darshanam for loss of vision in Aupsargika Lingnasha22. Acharya Sushruta used term Drishti runaddhi for loss of vision in Linganasha23.

c) Drishti in Modern View

In Modern Ophthalmology there are few structures related to vision which can be comparable to the description given in Ayurvedic texts for Drishti. Structures related to visual axis and vision are as following-

Cornea: Cornea is a clear, transparent and elliptical structure. The lens has nodal point (optical centre of lens) on its posterior part through which rays of light passes to retina.

Aqueous humour: The aqueous humour is a clear watery fluid filling the anterior chamber (0.25 ml) and posterior chamber (0.06 ml) of the eyeball. It plays an important metabolic role by providing substrates and by removing metabolites from the avascular cornea and lens. It maintains optical transparency.

Pupil: Pupil is central opening in the iris and its size varies between 1and 8mm. Constriction of pupil regulates the entry of light inside the eye and allows the retina to adapt to the changes in the illumination25.

Lens: The lens is a biconvex and transparent structure. The lens has nodal point (optical centre of lens) on its posterior part through which rays of light passes to retina.

<table>
<thead>
<tr>
<th>Name</th>
<th>Constituting factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Patala</td>
<td>Tejas + Jala (Tejojalaashrita)</td>
</tr>
<tr>
<td>2nd Patala</td>
<td>Mamsa (Mamsaashrita)</td>
</tr>
<tr>
<td>3rd Patala</td>
<td>Medas (Medoaashrita)</td>
</tr>
<tr>
<td>4th Patala</td>
<td>Asthi (Asthyaashrita)</td>
</tr>
</tbody>
</table>

According to Sushruta Samhita “5" Mandals11 in the eye ball -

Pakshma mandala.
Vartma mandala.
Shweta mandala.
Krishna mandala.
Drishti mandala.

“6” Sandhi12 in the eye ball-
Pakshma-Vartamagata Sandhi.
Vartama-Shuklagata Sandhi.
Shukla-Krishnagata Sandhi.
Krishna-Drishtigata.
Kaninaka Sandhi.
Apana Sandhi.

“6” Patalas13 in the eye ball-

Vartmagata Patalas-2
Akshigata Patalas-4
Retina: It is the innermost tunic of the eyeball and the most highly-developed tissue and consists of 10 layers. Grossly it is divided into two distinct regions: Posterior Pole and Peripheral Retina separated retinal equator. The posterior region of the retina is called the posterior pole, the posterior pole of the retina consists of two regions: the macula lutea and the optic disc.

Optic disc: The optic disc is also called the “blind spot” or the “physiological blind spot”. It is called this because there are no receptors in this part of the retina. This is where all of the axons of the ganglion cells exit the retina to form the optic nerve. There are no light sensitive rods or cones to respond to a light stimulus at this point.

Macula lutea: It is about 5.5 mm in diameter. Fovea centralis is the central depressed part of the macula. It is about 1.5 mm in diameter and is the most sensitive part of the retina. In its centre is a shining pit called Foveola (0.35 mm diameter) which is situated about 2-disc diameters (3 mm) away from the temporal margin of the disc and about 1 mm below the horizontal meridian. An area about 0.8 mm in diameter (including foveola and some surrounding area) does not containing retinal capillaries and is called foveal avascular zone (FAZ).

Visual Axis: Visual axis is the line joining the Gaze or fixation (O), nodal point (N), and the fovea (F).

Figure 1: Visual axis (OF)


Figure 2: Visual Pathway
**Drishti as Retina:** Drishti is made up of sara of Panchamahabhoot, but Teja mahabhoot is predominant in the form of Alochaka Pitta which is considered as light media for eye. Roopa with the help of teja travels into chakshu and then reached to chakshurendriya and then to chakshubudhhi where perception of the object occurs and finally perceived by atma which provide information of the object and all this can be considered as pathway for visual impulse received by eyes and thus enabling it to see.

**Indriyaartha (object has form)**

**Indriyadravya (light media)**

**Indriyaadhishthana (eyes)**

**Indriya (photoreceptor cells of retina (rods and cones)**

**Indriyabuddhi (transmission of image via visual pathway)**

**Atma (higher centre i.e. visual cortex)**

*d) Concept of physiological aspect of drishti*

Patalas are the main seat for the disease where the feature is impairment in vision. It may blurred vision for distance or near, metamorphopsia, diplopia and visual field defects. Acharya Bhela has described two types of alochaka pitta-

1. Chaksyu vaisheshika - The former is responsible for proper formation of image on the retina and transmission of impulses (conditions wherein the media of the eye and retina is involved).

2. Buddhi vaisheshika (Higher visual center-image analysed and perceived by buddhi)\(^{26}\).

*e) Concept of pathological aspects of drishti*

The diagnosis of a disease with impairment in the vision is based only on the symptoms. When prathamava and dwiteeya patala is invaded by the doshas, it is called as timira, triteeya patala is kacha and chaturtha patala is linganasha. These timira, kacha, linganasha are the progressive stages of a disease which starts with the blurring of vision, ending with complete loss of vision. Clinical application of concept of drishti Myopia: characterised by blurring of vision for distant objects\(^{27}\). This feature is seen in pratama patalagata dosha lakshana. Dosha is vata. Hence, vatajatimira line of management should be followed. Presbyopia is difficulty in near vision seen as a symptom in dwiteeya patalagata dosha. Dosha involved is vata. Vitreous degeneration, floaters are seen. This feature is seen in dwiteeya patalagata lakshana. Dosha is vata (responsible for degeneration). Diplopia wherein there will be double vision is seen as triteeya patalagata lakshana. Metamorphopsia which is seen in many conditions where there is distortion of vision\(^{28}\). This feature is seen in triteeya patalagata dosha lakshana (karna nasa kshi yuktani viparitani ca veekshyate). Dosha can be either vata or pitta. Visual field defects characterized by different pattern of vision loss. The pattern of visual field defect corresponds to the site of lesion in the visual pathway. For instance, if nasal fibres of right eye are affected it leads right temporal visual field defect\(^{29}\). In triteeya patalagata dosha, depending on the lodgement of dosha the corresponding side of vision will not be seen. For example, if the doshas are situated in the side of drishti then lateral part of field of vision is lost. This is seen as triteeya patalagata lakshana and also in sannipataja timira. Hence, sannipataja timira line of management should be followed.
The features of patalagata doshas are listed in the table below—

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Patalas</th>
<th>Lakshana</th>
<th>Interpretation of Symptoms and signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prathama</td>
<td>Disturbance in vision&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Blurred of vision</td>
</tr>
<tr>
<td>2</td>
<td>Dwiteeya</td>
<td>Patient sees objects like insects, hairs and webs, unable to perceive certain parts in a face, sees certain luminous objects like stars, objects which are near appears to be far and vice versa, unable to thread a needle&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Floaters, metamorphopsia, photopsia, loss of depth perception and presbyopia</td>
</tr>
<tr>
<td>3</td>
<td>Triteeya</td>
<td>There will be raga prapthi – different colours will be imparted to the patalas corresponding to the dosha involved. Vatadosha – reddish black, pitta – yellow or blue, kapha – white, rakta – red, sannipataja as multiple colours and parimlayi as yellow, red or blue&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Visual pathway defects, retinal tear or detachment, metamorphopsia. Raga prapthi to the patalas as any change in the general back ground. Example: vitreous haemorrhage – as pittaja, Retinitis pigmentosa as vataja.</td>
</tr>
<tr>
<td>4</td>
<td>Chaturtha</td>
<td>Complete loss of vision but still the patient sees bright objects like sun, moon and Lightening&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Conditions where in the patient is said to be legally blind, conditions where there is retinal traction leading to flashes.</td>
</tr>
</tbody>
</table>

IV. **Discussion**

In Ayurveda, Drishti is used as a broad terminology and is used accordingly in different aspects. From the present study it can be concluded that Drishti is not just a single entity but composed of many structures that can be correlated in modern ophthalmology. The structures which come across visual axis and their functional output in total can be taken as Drishti. In view of this definition the structures i.e. central part of Cornea, Pupil, Lens, Vitreous, Retina, Visual pathway all come under the broad view of Drishti along with functional outcome i.e. vision. For treating the diseases related with Drishti there should be proper knowledge of different terminologies and their practical implementation so that the basic aim of Ayurveda- to maintain the health of healthy person and to cure the unhealthy person can be achieved. In Ayurveda, Drishti is used as a broad terminology and is used accordingly in different aspects. From the present study it can be concluded that Drishti is not just a single entity but composed of many structures that can be correlated in modern ophthalmology. In this literary study we collected various data from the deferent Ayurvedic scriptures with the available commentaries, as well as text books of modern medical sciences, various articles for better understanding of the netra sharir and its comparison with contemporary science. Acharyas have explained prakriti also has described the anatomy of eye in relation to their shape, size of various anatomical components. Sushruta has explained seventy-six different kinds of eye diseases and their treatment in uttara tantra. The Netra execute both physiological functions roopagrahana and buddhigrahana as it is the seat of Alochaka pitta. It is predominant of tejo mahabhuta so, there is always dread of kapha to eye.

V. **Conclusion**

It is also said that all types of eye diseases originate from the Abhishyandha. Therefore, the wise doctor should first treat the disease Abhishyandha (Prayena sarve nayanaamayastu bhavantyaabishand-nimittamula)<sup>34</sup>. The eye sees the images with the help of mind not by the eye (itself) and the eye dose not(actually) see the images when the mind is perturbed even if it (physically) sees them. It has to be understood what it implies in relation to where the word drishti is being used. As explained above, in context of anatomy it should be referred as pupil, in context of kanch, timir, linganaash (dritishtagata rogas) it should be considered as intraocular lens whereas in pitta vidagdha drishti, shleshma vidagdha drishti etc. dritishtagada rogas it must be taken as optic nerve or retina as a whole.

**References Références Referencias**


27. Parson’s diseases of the eye, Ramanjitsihota, radhika tendon, 22nd edition, Elsevier publication, Haryana, 2015, pg. 28, 29, 30
28. Parson’s diseases of the eye, Ramanjitsihota, radhika tendon, 22nd edition, Elsevier publication, Haryana, 2015, pg. 71
29. Parson’s diseases of the eye, Ramanjitsihota, radhika tendon, 22nd edition, Elsevier publication, Haryana, 2015, pg. 58, 343, 435, 256
30. Dr. Anant Ram Sharma, Sushruta Samhita edited with Susrutavimarsini Hindi Commentary, Uttar Tantra 7st chapter Drishtirogavigyaniyaadhyaya 7/6, Varanasi, Chaukhambha Sanskrit Sansthan, reprint edition; 2013. p.54
32. Dr. Anant Ram Sharma, Sushruta Samhita edited with Susrutavimarsini Hindi Commentary, Uttar Tantra 7st chapter Drishtirogavigyaniyaadhyaya 7/11-14, Varanasi, Chaukhambha Sanskrit Sansthan, reprint edition; 2013. p.55
33. Dr. Anant Ram Sharma, Sushruta Samhita edited with Susrutavimarsini Hindi Commentary, Uttar Tantra 7st chapter Drishtirogavigyaniyaadhyaya 7/15-17, Varanasi, Chaukhambha Sanskrit Sansthan, reprint edition; 2013. p.56
34. Dr. Anant Ram Sharma, Sushruta Samhita edited with Susrutavimarsini Hindi Commentary, Uttar Tantra 6st chapter Sarvarogavigyaniyaadhyaya 6/5, Varanasi, Chaukhambha Sanskrit Sansthan, reprint edition; 2013. p.43
This page is intentionally left blank
Ceftriaxone-Induced Gallbladder Stones in Children

By Dr. Maryam Al Saidi, Dr. Samiya Al Hashmi, Dr. Nuha AlTahir & Dr. Hilal AL Hashami

Abstract- Gallbladder stones in children are one complication, most seen in such diseases as hemolytic disease, liver disease, and obesity. They can be a secondary complication of long duration used of antibiotics like ceftriaxone. However, Gallbladder stone and together with sludge themselves is unusual within the children population. We were observed in some instances by a particular sort of antibiotic that is being referred by Ceftriaxone. It is the third-generation cephalosporin with a wide broad-spectrum utilized in treating multiple complicated infected organisms. Here, in this study, we report three cases of children with age degrees from eleven months to seven years who have been treated with high doses and long duration of ceftriaxone for complicated systemic bacterial infection. The purpose of this study was to determine the dose and duration of ceftriaxone in children who developed gallbladder stones after treating complex bacteria with ceftriaxone and to evaluate the outcome of the treatment in these patients.

Keywords: ceftriaxone, gallbladder stone, child, complication.

GJMR-F Classification: NLMC Code: WI 140

Strictly as per the compliance and regulations of:
Abstract - Gallbladder stones in children are one complication, most seen in such diseases as hemolytic disease, liver disease, and obesity. They can be a secondary complication of long duration used of antibiotics like ceftriaxone. However, Gallbladder stone and together with sludge themselves is unusual within the children population. We were observed in some instances by a particular sort of antibiotic that is being referred by Ceftriaxone. It is the third-generation cephalosporin with a wide broad-spectrum utilized in treating multiple complicated infected organisms. Here, in this study, we report three cases of children with age degrees in treating multiple complicated infected organisms. The purpose of this study was to determine the dose and duration of ceftriaxone in children who developed gallbladder stones after treating complex bacteria with ceftriaxone and to evaluate the outcome of the treatment in these patients.

Keywords: ceftriaxone, gallbladder stone, child, complication.

I. Introduction

Gallbladder stone has been reported in both adults and children due to a different complication of illness, mainly hemolytic disorder, procedure, and even with the long-term duration use of antibiotics which is being seen by ceftriaxone. It is seen as much less common in children compared to adults, however, being asymptomatic as compared to children wherein it can be symptomatic. Ceftriaxone is the principal agent of third-generation of the cephalosporin with a broad-spectrum effect and is used for the treatment of severe bacterial infections like osteomyelitis, Gastrointestinal, and meningitis in the children population [4,10]. It is far extensively distributed in most body tissues and fluids and can penetrate blood-brain barriers into the meninges [3,4,14]. Its characteristic can also have excreted by the urine, and 40 % is secreted by the bile duct [3], because of the lengthy plasma half-life that may be administered once daily and each 12-hour regimen in case of complex infection in some children. Most medication has adverse drug reactions, including ceftriaxone that has more being reported by a causative agent for pseudolithiasis either in the gall bladder or renal tract [4,5,14]. It is named reversible ceftriaxone-associated Cholelithiasis, additionally biliary pseudolithiasis or reversible Cholelithiasis based on Ultrasound findings [10]. This name is given by radiological image because it is a transient condition, which resolves after discontinuation of the causative agent. In this study, we evaluated children with ceftriaxone-associated Gall bladder stone discovered incidentally in abdomen Ultrasound examination. It includes three children with gallstones on Ultrasound of the abdomen after presentation with short duration severe abdomen pain and with recent concurrent long-duration use of ceftriaxone.

II. Case Description

a) Case one

An eleven months-old boy previously well was presented to the Emergency department with an impression of meningoencephalitis with a history of a few days of fever, seizures, and hemorrhagic rash subsequently develop septic shock with a picture of Disseminated intravascular coagulation (DIC) and acute kidney injury. The investigation was done with high White blood cell (WBC of 23,10^9/l), high C-Reactive Protein (CRP of 153 mg/l), and Liver Function Test (LFT) within normal range. Lumbar Puncture showed: cerebrospinal fluid (CSF) microscopy no organism, White Blood Cell of 4 cell/mm², high Red Blood Cell of 3320 cell/mm², protein 2.73g/L, and glucose of 2.9 mmol/L. CSF culture was negative, blood culture initially negative, but repeated blood culture was positive for *Streptococcus pneumonia*. Radiological study with initial head-CT scan showed ischemic change then repeated after few days showed acute right intraparenchymal bleeding the right parietal region measuring 15*15*8 mm surrounded by a thin rim of enema. Magnetic resonance imaging (MRI) of the head showed dilated ventricular system. The diagnosis of *Streptococcus pneumonia* Meningoencephalitis was confirmed by MRI finding, and a ventriculoperitoneal (VP) shunt was inserted by a neurosurgery team. Ceftriaxone therapy started for around four weeks then shifted to levofloxacin as the patient developed acute abdominal pain with irritability. Abdomen Ultrasound was done by a pediatric radiologist, and it showed a distended gall bladder with a clump of soft calculi, which was an indication to stop ceftriaxone. A liver function test was done by the general pediatric team after ten days of ceftriaxone with ALT 20 IU/L and ALP 226 IU/L. After two weeks from stopping, ceftriaxone, abdomen ultrasound repeated and showed
Single mobile echogenic focus; Gall bladder stone measures 8mm. Child abdominal pain improved with levofloxacin.

**Figure (1):** The finding of abdomen US a patient treated with ceftriaxone for complicated central nervous infection for long duration.

**b) Case Two**

Two years old boy is known to have asthma on Montelukast. He was presented to the pediatric Emergency Department at Royal hospital with a history of fever for two days. It was documented high-grade fever 39°C, not respond to antipyretic. He also had a history of vomiting and productive cough associated with lethargy and reduced activity for two days. He was lethargic, irritable, dehydrated, had a large head with head circumference above 97%, and neck stiffness on review. Investigation showed, leucocytosis of 28,10^9/l, mainly neutrophils with 24,10^9/l in complete blood count (CBC) and high C reactive protein of 171 mg/L, lumbar puncture showed turbid cerebellar spinal fluid CSF with high white blood cell WBC 453 x 10^9/L and low glucose. Cerebrospinal fluid (CSF) culture revealed *streptococcus pneumonia*, the respiratory panel was positive for parainfluenza 3. The first radiology image was a Non-contrast CT Scan of the head which showed mild brain edema. Head MRI indicates Right frontal-parietal meningitis with bilateral subdural effusion no abscess. The diagnosis of complicated *streptococcus pneumonia* meningitis with bilateral subdural effusion was given to this infant. He treated with a long course of intravenous Ceftriaxone. After week four of treatment, it noted that the child complained of abdominal pain. The initial Ultrasound abdomen was done and reported normal, then repeated after the child complained of abdominal pain, and it revealed gallbladder stones, for that it decided to change ceftriaxone after completed four months to levofloxacin to continue for another 3-6 weeks of duration. As noted, it was associated with a deranged liver function test (LFT) with high alkaline phosphate (ALP) of 285 IU/L, GGT=42 IU/L and alanine transaminase (ALT) of 91 IU/L which is initially normal LFT. Follow up; Abdomen Ultrasound showed improvement after changing ceftriaxone to Levofloxacin. Liver Enzyme also improved.

**Figure (2):** The finding of abdomen US in a patient treated with ceftriaxone for complicated central nervous infection for a long duration.
c) Case Three

A seven-year old girl who was previously well with no past medical illness. She presented to an orthopedic clinic with a brief history of left knee pain and swelling and was diagnosed with an impression of left distal femur and proximal tibia osteomyelitis. Based on blood laboratory findings and radiological findings of MRI of femurs and tibias that revealed bone marrow edema in the lateral femoral condyle and bony abscess in the metaphysis of the left distal femur and proximal tibia, an impression of acute on subacute changes of osteomyelitis in the lateral femoral condyle, she was treated for three weeks with ceftriaxone. She was doing well until three weeks after beginning ceftriaxone, when she went to the ER with a one-day bout of severe abdominal pain and vomiting. She was admitted and evaluated by a pediatric surgeon to rule out any intestinal obstructions. An abdomen ultrasound (US) revealed that she had multiple tiny calculi in her gallbladder. Laboratory investigations done at the time of presentation showed normal total blood count with White blood cell 11 * 10⁹/l, Haemoglobin (HB) 11.7 g/dl, Normal Liver function test, and Normal amylase level. She referred to pediatric gastroenterology and pediatric infectious diseases for further management and her antibiotic was changed to clindamycin. She continued on clindamycin, and her symptoms improved. Abdomen ultrasound has not yet been repeated after switching from ceftriaxone to clindamycin.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>sex</th>
<th>Ceftriaxone therapy</th>
<th>Biliary complication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dose (mg/kg)</td>
<td>Duration(days)</td>
</tr>
<tr>
<td>1</td>
<td>11months</td>
<td>M</td>
<td>100 mg/kg/days</td>
<td>21 days</td>
</tr>
<tr>
<td>2</td>
<td>2years</td>
<td>M</td>
<td>100 mg/kg/days</td>
<td>120 days</td>
</tr>
<tr>
<td>3</td>
<td>7years</td>
<td>F</td>
<td>100 mg/kg/days</td>
<td>26 days</td>
</tr>
</tbody>
</table>

[Table 1]: Characteristics of ceftriaxone duration and dose with biliary complications in the three patients.

**Figure (3):** The finding of abdomen US the patient who treated with ceftriaxone for bone infection.
III. Discussion and Literature Review

There are limited studies that looked into ceftriaxone-induced gallstones within the children population. Within the most literature review, gallbladder stone occurs because of organic cause or illness, but few numbers reported predisposing factor with the specific type of antibiotics uses that presented as symptomatic illness. Ceftriaxone is a broad-spectrum antimicrobial agent. It is one among the third-generation cephalosporin. It is a broad-spectrum effect against the most bacterial infection, mainly causing meningitis, gastrointestinal, and osteomyelitis. As we all know that supported different literature reviews, the exact pathology of it was unclear [14,15]. Some studies explained because of the genetic/genome variation on the UGT1A1 gene, which is UGT1A1 encodes on the enzyme of UDP-glucuronosyltransferase (UDP). This enzyme acts on glucuronidation and formation of bile salts that transform small lipophilic molecules, (i.e., steroids, bilirubin, and drugs) the water-soluble (Fretzayas et al., 2011) [14,15].

In our study, we reported three cases of children with age ranges from the age of eleven months to seven years treated in tertiary hospital for severe bacterial infection and one in all children female at the age of seven years was referred from orthopedic clinic to pediatric infectious diseases services for follow up and further management of her acute osteomyelitis of Left distal femur and proximal tibia. The remaining two cases treated with a high dose of ceftriaxone 80-100mg/kg/twice daily dose for complicated meningitis. The three cases presented with nausea, vomiting, abdominal pain, and irritability during the third to fourth week of ceftriaxone administration. They were admitted and evaluated by different teams (General pediatric, pediatric infectious disease, pediatric surgeon, and gastroenterology team). All basic blood investigations were done, including full blood count and liver enzymes at time of admission; abdomen US was also done. We found one case which was treated with ceftriaxone for meningitis had a deranged liver function (high aminotransferase ALT = 91IU/L and high GGT=42IU/L). The opposite two children had normal range of laboratory finding with Blood count and Liver enzyme. Abdomen Ultrasound, for two of children, showed with distended gallbladder with multiple tiny calculi/ clump of sludge or soft calculi. The rest case was a normal finding of abdomen us, which was done at three weeks of used ceftriaxone. Later, abdomen US repeated and showed with the GB is filled with multiple small calculi, average=5mm, nolibiliary dilation. The pediatric surgery team was also involved, but none of the patients required any surgical intervention. After abdomen US finding, ceftriaxone discontinued for all cases. Within the two patient of meningitis, ceftriaxone change to Levofloxacin, and therefore the rest case of osteomyelitis was turned into clindamycin. All children didn’t require the other medication. All investigations normalized after discontinuing ceftriaxone. Abdomen ultrasound repeated and showed improvement in gall stones together with normalized the liver enzymes. Our review found that almost all of the biliary pseudolithiasis were self-resolving after cessation of ceftriaxone. Most Literature (Pacifici, 2019) reported the common adverse reaction of ceftriaxone is Gastrointestinal symptoms (nausea, vomiting with most predominant abdomen pain). We noticed that all told three patients together with same the incidental finding of pseudolithiasis in abdomen Ultrasound [4,15]. The same findings were reported in an Iranian study; different predisposing factors cause Cholelithiasis in children, which may be an organic illness such as Haemolytic disease, Hepatobiliary disease, obesity, metabolic syndrome, and secondary to ceftriaxone use that is reported in most cases in the children group as represented with a high 27.3% during a study compared to hematological disorder which reported 13.Gokce et al. [5] reported that gallstones were resolved by using Ursodeoxycholic acid (UDCA) treatment in 29.4% of symptomatic children. Hypercalcemia, kidney failure, a high dose of ceftriaxone (> 200mg/kg/day), and gallbladder stasis are all risk factors that determine whether or not ceftriaxone causes pseudolithiasis [10]. In our three cases, only one risk factor, which was noticed in our case, is used a high dose of ceftriaxone along with prolonging duration of more than three weeks to four months. Palanduz, et al. [11] reported in their study that 118 children were admitted to hospital for severe infection and received intravenous ceftriaxone at a dose of 100 mg/kg /day for three weeks. On days one, seven, and fourteen, an ultrasound abdomen was performed at regular intervals to monitor the adverse effects of ceftriaxone. After 14 days of intravenous ceftriaxone, twenty children (17%), all asymptomatic, had abnormal ultrasound findings: 8 had gallbladder sludge, and 12 had pseudolithiasis. By discontinuing ceftriaxone, the abnormalities spontaneously resolved within two weeks after stopping ceftriaxone. However, Cholelithiasis may have very different causative reasons in childhood. It is frequently detected by using abdominal ultrasound in symptomatic children. Most symptomatic cases are resolved after cessation of ceftriaxone use. Ursodeoxycholic acid is now commonly used as an alternative to surgery to treat cholelithiasis, particularly in children with biliary sludge. They concluded that Ceftriaxone-associated biliary pseudolithiasis is usually asymptomatic and was rapidly reversible after cessation of therapy. It has to be monitored in children who receive high dose and long term treatment by blood investigations that include fullblood count, liver function test, renal function test, and an ultrasound of the abdomen with different intervals.
Ceftriaxone is one of the third-generation cephalosporin with a broad spectrum effect against complex bacterial infection, one factor-induced gallbladder stone among the adult and children population. The correct diagnosis of ceftriaxone-induced gallstone was usually delayed as most of the patients asymptomatic and most cases were detected only by radiological findings. They were promoting proper clinical assessment with radiological findings in such cases where risk factors are present to prevent complications. The complication resolved spontaneously after discontinuation of the causative antibiotics.

Abbreviations

UGT1A1: UDP-glucuronosyltransferase 1 family gene
UDCA: ursodexoxycholic acid
UGT: UDP-glucuronosyltransferase
US: ultrasounds
ALT: -Alanine transaminase
GGT: Gamma-Glutamyl Transferase
MRI: Magnetic resonance imaging
CT scan: Computed tomography
CSF: cerebrospinal fluid

Conflict of Interests: The authors declare no conflict of interest.

Bibliography


This page is intentionally left blank
Survival Analysis for Pancreatic Cancer Patients using Cox-Proportional Hazard (CPH) Model

By Aditya Chakraborty & Chris P. Tsokos

Abstract- Pancreatic cancer is comparatively rare but extremely lethal. In the United States, pancreatic cancer is the 4th leading cause of cancer death, and in Europe, it is the 6th. Though Pancreatic cancer remains incurable if detected late, research into improving the therapeutic strategy has increased significantly in recent years. However, it is ambiguous if sustained improvements have been achieved by identifying the most prominent risk factors responsible for cancer. In this article, we studied the survival times of 677 pancreatic cancer patients with fifteen risk factors. The semi-parametric Cox proportional hazard (CPH) model was used to examine the covariate effect taking into account all of the statistically significant risk factors and their significant twoway interactions. A careful and rigorous assessment of the risk factors based on the AIC of the stepwise selection technique revealed seven risk factors, and ten interaction terms are statistically significantly contributing to the survival times. The final Cox-PH model was well-validated and satisfied all the key assumptions. The identified risk factors and their interactions are ranked according to the prognostic effect on the survival time based on the hazard ratio. We found the most contributing risk factor is the combined effect of patients with emphysema and cancer stage regional with a hazard ratio (HR) = 8.84.

Keywords: pancreatic cancer, cox-PH model, pancreatic survival function.

GJMR-F Classification: NLMC Code: WI 800
Survival Analysis for Pancreatic Cancer Patients using Cox-Proportional Hazard (CPH) Model

Aditya Chakraborty & Chris P. Tsokos

Abstract- Pancreatic cancer is comparatively rare but extremely lethal. In the United States, pancreatic cancer is the 4th leading cause of cancer death, and in Europe, it is the 6th. Though Pancreatic cancer remains incurable if detected late, research into improving the therapeutic strategy has increased significantly in recent years. However, it is ambiguous if sustained improvements have been achieved by identifying the most prominent risk factors responsible for cancer. In this article, we studied the survival times of 677 pancreatic cancer patients with fifteen risk factors. The semi-parametric Cox proportional hazard (CPH) model was used to examine the covariate effect taking into account all of the statistically significant risk factors and their significant two-way interactions. A careful and rigorous assessment of the risk factors based on the AIC of the stepwise selection technique revealed seven risk factors, and ten interaction terms are statistically significantly contributing to the survival times. The final Cox-PH model was well-validated and satisfied all the key assumptions. The identified risk factors and their interactions are ranked according to the prognostic effect on the survival time based on the hazard ratio. We found the most contributing risk factor is the combined effect of patients with emphysema and cancer stage regional with a hazard ratio (HR) = 8.84. The most significant highest contributing individual risk factor is diabetes with a hazard ratio of 2.39, followed by ibuprofen with a hazard ratio of 1.83. This study offers prognostic and therapeutic significance for further enhancement in the treatment strategy of pancreatic cancer.

Keywords: pancreatic cancer, cox-PH model, pancreatic survival function.

I. INTRODUCTION

In the domain of the lethal carcinogenic diseases affecting humans, pancreatic cancer is one of the fatal cancers and continues to be a crucial unsolved health problem at the start of the 21st century. Because of the high fatality rates, pancreatic cancer incidence rates are almost equal to mortality rates (22). According to the current health science researchers, this disease causes approximately 30,000 deaths per year in the USA. (1). It is the fourth principal reason for cancer death in the USA and leads to an estimated 227,000 deaths per year worldwide. The incidence and number of deaths caused by pancreatic tumors have been gradually increasing, even as incidence and mortality of other common cancers have been declining. Despite developments in detection and management of pancreatic cancer, only about 4% of patients will live five years after diagnosis, (2). The normal pancreas consists of digestive enzyme-secreting acinar cells, bicarbonate-secreting ductal cells, centroacinar cells that are the geographical transition between acinar and ductal cells, hormone-secreting endocrine islets and relatively inactive stellate cells. The majority of malignant neoplasms of the pancreas are adenocarcinomas. Rare pancreatic neoplasms include neuroendocrine tumors (which can secrete hormones such as insulin or glucagon) and acinar carcinomas (which can release digestive enzymes into the circulation). Particularly, ductal adenocarcinoma is the most frequent kind of malignancy of the pancreas; this tumor (commonly referred to as pancreatic cancer) presents a substantial health problem, with an estimated 367,000 new cases diagnosed worldwide in 2015 and an associated 359,000 deaths in the same year(3)(4). After the detection of pancreatic cancer, doctors usually perform some additional tests to understand better if cancer has been spread or the spreading area of cancer. Different imaging tests, such as a PET scan, can help doctors identify the presence of cancerous growths. With these tests, doctors try to establish cancer’s stage. Staging helps explicate how advanced the cancer is. It also assists doctors in deciding the treatment options. The following are the description of the stages used in our dataset according to the definition of the Surveillance, Epidemiology, and End Results (SEER) database.
1. **Localized**: There is no sign that the cancer has spread outside of the pancreas.

2. **Regional**: The cancer has spread from the pancreas to nearby structures or lymph nodes.

3. **Distant**: The cancer has spread to distant parts of the body such as the lungs, liver or bones.

The following Figure 1 shows the different parts of the pancreas.

**Figure 1**: Different Parts of the Pancreas

Although, in most cases, pancreatic cancer remains incurable, researchers have focused on how to improve the survival times of patients diagnosed with pancreatic cancer. Cox proportional hazard model/Cox model (5) has been used extensively in the literature of cancer research to address the hazard of an individual patient with respect to specific risk factors. It is also useful to assess the association between different treatments and the survival time of patients. Perera and Tsokos (6) developed a statistical model with Non-Linear Effects and Non-Proportional Hazards for Breast Cancer Survival Analysis. In their study, the authors have identified the effects of age and breast cancer tumor size at diagnosis on the hazard function, which have a non-linear effect. Also, they have addressed the different assumptions of the proportional hazard model. Asano, Hirakawa, and Hamada (7) used an imputation-based receiver operating characteristic curve (AUC) to evaluate the predictive accuracy of the cure rate from the PH cure model. They also illustrated the estimation of the imputation-based AUCs using breast cancer data. Yong & Tsokos (8) have evaluated the effectiveness of widely used Kaplan-Meier (KM) model, non-parametric Kernel density (KD) models with the Cox PH model, using both Monte Carlo simulations on the breast cancer data. Du, Li et al. (2018) (9) compared a flexible parametric survival model (FPSM) and Cox model using Markov transition probabilities from a cohort study data investigating ischemic stroke outcomes in Western China. The FPSM produced
hazard ratio and baseline cumulative hazard estimates similar to those obtained using the Cox proportional hazards model. Mamudu & Tsokos (20) developed a semi-parametric Cox model for Multiple Myeloma Cancer (MMC) patients and addressed the validity of the assumptions of the model.

In our study, we used the semi-parametric Cox-PH survival analysis of the survival times to estimate the survival rate of patients diagnosed with pancreatic cancer. We utilized the Cox-PH model to analyze the proportion of survival time, taking into account the fifteen risk factors that are identified in section 2.1. We assessed the relationship between the proportion of survival time as a function of the attributable risk factors and two-way interactions based on the Cox proportional hazard (PH) model. The significant attributable risk factors identified were meticulously investigated and selected based on the step-wise model selection method, with the final model representing the model with the least AIC. The final Cox-PH model was validated to satisfy all the main assumptions of the Cox-PH model.

II. Methodology

a) Data Description

The data for our study has been obtained from The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial system of the National Cancer Institute (NIH) database. The data contains information on patients diagnosed with pancreatic adenocarcinoma. We are concerned with the survival time (in days) and cause-specific death (deaths due to pancreatic cancer) for each patient. The survival time of patients is one of the most important factors used in all cancer research. It is important to evaluate the severity of cancer, which helps to decide the prognosis and help identify the correct treatment methods. There were a total of 677 patient information in our study after eliminating the missing observations for which several risk factors were missing. In our study, the response variable is the survival time of patients (in days). There are a total of fifteen risk factors used in our survival model. Twelve of them are categorical, and three of them are numeric variables. The description of the risk factors is as follows.

1. Age (Numeric) \( (X_1) \): Age of diagnosis of the patient.
2. Stage (Categorical) \( (X_2) \): Pancreatic Cancer Stages, categorized as a) localized, b) regional, and c) distant
3. Aspirin (Categorical) \( (X_3) \): Does the person use Aspirin Regularly?
4. Ibuprofen (Categorical) \( (X_4) \): Does the person use Ibuprofen Regularly?
5. Relatives (Categorical) \( (X_5) \): The number of first-degree relatives with pancreatic cancer.
6. Diabetes (Categorical) \( (X_6) \): Did the patient ever have diabetes?
7. Heart attack (Categorical) \( (X_7) \): Did the participant ever have coronary heart disease or a heart attack?
8. Emphysema (Categorical) \( (X_8) \): Did the patient ever have emphysema?
9. Sex (Categorical) \( (X_9) \): Sex of the individual.
10. BMI (numeric) \( (X_{10}) \): Current Body Mass Index (BMI) at Baseline (In lb/in2)
11. Cigarette Years (numeric) \( (X_{11}) \): The total number of years the patient smoked.
12. Diverticulosis (Categorical) \( (X_{12}) \): Did the participant ever have diverticulitis or diverticulosis?
13. Smoke (Categorical) \( (X_{13}) \): Has the patient ever smoked cigarettes regularly for six months or longer?
14. Gallbladder (Categorical) ($X_{14}$): Did the individual ever have gall bladder stones or inflammation?

15. Hypertension (Categorical) ($X_{15}$): Did the individual ever have high blood pressure?

A schematic diagram of the data used in our study with the description of risk factors is shown in Figure 2, below.

![Pancreatic Cancer Data with Relevant Risk Factors](image)

**Figure 2:** Pancreatic Cancer Data with Relevant Risk Factors

As the above Figure illustrates, we see that twelve out of fifteen risk factors are categorical, having two or more categories. Before we proceed with our main analysis, it is very important to investigate if there is any statistically significant difference between the survival times of male and female patients diagnosed with pancreatic cancer. If any significant differences are found, separate analyses for each gender should be performed. To answer this question, we used the non-parametric Wilcoxon rank-sum test with continuity correction and obtained a p-value of .47, indicating that there is not enough sample evidence to reject the following null hypothesis ($H_0$) at a 5% level of significance.

$H_0$: There is no statistically significant difference between the survival times of male and female patients.

Thus we proceeded with our analysis and modeling by combining the male and female data together to constitute our sample size.

### III. Brief Description of Cox Proportional Hazard (CPH) Model

The Cox PH model, proposed by Sir David Cox, is a statistical method that can be used for survival-time (time-to-event) outcomes on one or more risk factors and their interactions. In survival analysis, the Cox model has been widely recommended for semi-parametric modeling of the survival time relationship as a function of the risk factors. Kleinbaum & Klein (10) gives a good introductory review of the background and methodology, and more detailed descriptions have been provided by Kalbeisch , and Prentice (11)(12). In this section, we give a brief review of the Cox proportional hazards model. An important aspect of the Cox PH model is the hazard function $h(t)$. It measures the rate of the event of occurrence (death) as a function of time $t$. We define the hazard function as follows; Let random variable $T$ denotes the survival time with cumulative density function $F_T(t)$, given by

$$F_T(t) = P(T \leq t) = \int_0^t f(t)dt,$$
Survival Analysis for Pancreatic Cancer Patients using Cox-Proportional Hazard (CPH) Model

where \( f(t) = \frac{dF_T(t)}{dt} \) is the probability density function (pdf) of the random variable \( T \). The survival function at time \( t \) is defined as:

\[
S(t) = P(T \geq t) = 1 - F_T(t) = \int_t^\infty f(t)\,dt .
\]  

(1)

\( S(t) \) gives the probability that a specific individual would survive beyond time \( t \). Since \( S(t) \) is a probability, \( 0 \leq S(t) \leq 1 \) and \( S(0) = 1 \), for \( T \geq 0 \) from (1) we have,

\[
f(t) = \frac{dF_T(t)}{dt} = \frac{-dS(t)}{dt} .
\]  

(2)

For continuous survival data, the hazard function plays a very important role. It aims to quantify the instantaneous risks that an event will occur at time \( t \). It is defined as the follows:

\[
h(t) = \lim_{\Delta t \to 0} \frac{P\{t \leq T < t + \Delta t \mid T \geq t\}}{\Delta t} = \lim_{\Delta t \to 0} \frac{P\{t \leq T < t + \Delta t\}}{\Delta t} \frac{1}{S(t)}
\]  

(3)

Combining (2) and (3), we obtain,

\[
h(t) = -\frac{d}{dt} \log\{S(t)\} .
\]  

(4)

Integrating both sides of equation (4) gives an expression for the survival function \( S(t) \) in terms of the hazard function \( h(t) \). That is,

\[
S(t) = \exp\left[-\int_0^t h(u)\,du\right].
\]  

(5)

Now, from (3) and (5) we can express the pdf \( f(t) \) as a function of \( S(t) \) and \( h(t) \) given by,

\[
f(t) = h(t)\exp\left[-\int_0^t h(u)\,du\right].
\]  

(6)

From (3) the cumulative hazard function \( H(t) \) can be expressed as:

\[
H(t) = \int_0^t h(u)\,du = -\ln S(t) .
\]  

(7)

Now, suppose \( X_i = (X_{i1}, X_{i1}, \ldots, X_{ip}) \) are the realized values of the risk factor for the \( i^{th} \) subject. Then, the Cox PH model (not including time-dependent risk factors or non-proportional hazards) can be expressed in term of the hazard as:

\[
h_i(t) = \lambda_0(t)\exp\left[\sum_{j=1}^p \beta_j X_{ij} + \sum_{j \neq k} \eta_{jk} X_{ij} X_{ik}\right], \ j, k = 1, 2, \ldots, p.
\]  

(8)

In the above expression, \( \lambda_0 \) is called the baseline hazard which can be thought of as the hazard function for an individual for which all value of the risk factors are 0. \( \beta_j \) measures the impact of \( X_{ij} \) on \( h_i(t) \). \( \eta_{jk} \) is the interaction coefficient between \( j^{th} \) and \( k^{th} \) risk factor of the \( i^{th} \) individual and
measures the impact of $X_{ij}X_{ik}$ on $h_i(t)$. From (8), it is clear that the individual hazard is a function of the risk factors and their interactions and is connected through baseline hazard. From (8), we can write,

\[ \ln \left\{ \frac{h_i(t)}{h_k(t)} \right\} = \left[ \sum_{j=1}^{p} \beta_j X_{ij} + \sum_{j \neq k} \eta_{jk}X_{ij}X_{ik} \right], \quad j \neq k \tag{9} \]

From the above expression we see that the ratio of log hazard of the $i^{th}$ and $k^{th}$ individual is constant over time. Thus, the name \textit{proportional} in the Cox PH model. We interpret the hazard ratio (HR) in the following ways:

1. HR = 1; implies that there is no hazard effect. Thus, the risk factors have no relationship with the event probability, thus, no influence on the length of survival.
2. HR > 1 (i.e. equivalently $\beta_i > 0$), implies an increase in hazard. That is, the risk factors have a positive association with the event probability, thus, a negative association with the length of survival (bad prognostic factor).
3. HR < 1 (i.e. equivalently $\beta_i < 0$), implies a decrease in hazard. That is, the risk factors are negatively associated with the probability of the event, thus, positively associated with the length of survival (good prognostic factor).

A detailed description of the hazard ratio have been provided in (14) (15).

\[ \ln \left\{ \frac{h_i(t)}{h_k(t)} \right\} = \left[ \sum_{j=1}^{p} \beta_j X_{ij} + \sum_{j \neq k} \eta_{jk}X_{ij}X_{ik} \right], \quad j \neq k \tag{9} \]

From the above expression we see that the ratio of log hazard of the $i^{th}$ and $k^{th}$ individual is constant over time. Thus, the name \textit{proportional} in the Cox PH model. We interpret the hazard ratio (HR) in the following ways:

1. HR = 1; implies that there is no hazard effect. Thus, the risk factors have no relationship with the event probability, thus, no influence on the length of survival.
2. HR > 1 (i.e. equivalently $\beta_i > 0$), implies an increase in hazard. That is, the risk factors have a positive association with the event probability, thus, a negative association with the length of survival (bad prognostic factor).
3. HR < 1 (i.e. equivalently $\beta_i < 0$), implies a decrease in hazard. That is, the risk factors are negatively associated with the probability of the event, thus, positively associated with the length of survival (good prognostic factor).

A detailed description of the hazard ratio have been provided in (14) (15).

\[ \ln \left\{ \frac{h_i(t)}{h_k(t)} \right\} = \left[ \sum_{j=1}^{p} \beta_j X_{ij} + \sum_{j \neq k} \eta_{jk}X_{ij}X_{ik} \right], \quad j \neq k \tag{9} \]

From the above expression we see that the ratio of log hazard of the $i^{th}$ and $k^{th}$ individual is constant over time. Thus, the name \textit{proportional} in the Cox PH model. We interpret the hazard ratio (HR) in the following ways:

1. HR = 1; implies that there is no hazard effect. Thus, the risk factors have no relationship with the event probability, thus, no influence on the length of survival.
2. HR > 1 (i.e. equivalently $\beta_i > 0$), implies an increase in hazard. That is, the risk factors have a positive association with the event probability, thus, a negative association with the length of survival (bad prognostic factor).
3. HR < 1 (i.e. equivalently $\beta_i < 0$), implies a decrease in hazard. That is, the risk factors are negatively associated with the probability of the event, thus, positively associated with the length of survival (good prognostic factor).

A detailed description of the hazard ratio have been provided in (14) (15).

\[ \ln \left\{ \frac{h_i(t)}{h_k(t)} \right\} = \left[ \sum_{j=1}^{p} \beta_j X_{ij} + \sum_{j \neq k} \eta_{jk}X_{ij}X_{ik} \right], \quad j \neq k \tag{9} \]

IV. Statistical Data Analysis and Survival Modeling

We now proceed to develop our most parsimonious statistical model using Cox PH. We initially started by fitting the Cox-PH model to the survival times $t$ as a function of all fifteen risk factors given in Figure 2 together with their two-way interactions. So, there were fifteen risk factors and $\binom{15}{2} = 105$ two-way interaction terms. We used a stepwise model selection procedure to select the best model with the minimum Akaike information criterion (AIC $= 2\ln(L) + 2k$, where $L$ is the value of the maximum likelihood function of the model and $k$ represents the number of estimated model parameters)(13). AIC gives an estimation of the relative amount of information missing in the model; hence, the smaller the AIC value, the better the quality of the model. It also deals with the risk associated with overfitting or under-fitting the model. One of the most important assumptions of the Cox PH is proportionality. Initially, all of the risk factors and two-way interactions except age satisfied the assumption. The range of the variable age was [50-90). So, we divided the range into two categories, say [50,70), and [70,90). Now, we use \textit{stratification} on the variable age. Stratification is one of the tools used by researchers when one of the risk factors does not satisfy the proportionality assumption. The stratification will produce hazard ratios for all other risk factors in the presence of two hazards intrinsic to the level of age. Since age violated the proportional hazards assumption, stratifying it will help meet the PH assumption and provide more valid estimates for all other risk factors. The stratified model allows the baseline hazard $\lambda_0(t)$ to vary between strata but controls the effect of the risk factors to be the same for each stratum. For each subject in strata $s, s = 1, 2$, we have from (8),

\[ h_i(t) = \lambda_{0s}(t)exp\left[ \sum_{j=1}^{p} \beta_j X_{ij} + \sum_{j \neq k} \eta_{jk}X_{ij}X_{ik} \right], \quad j, k = 1, 2, \ldots, p. \quad (s = 1, 2) \tag{10} \]

However, it is not possible to get an estimate of the risk factor (age) separately after stratification. The following Figure 3 illustrates the survival curve for the two age groups.
We observe from Figure 3 that the age group [70,90) (highlighted in pink) is much more vulnerable than the age group [50,70) (highlighted in blue) in terms of survival probabilities. That is, a randomly selected patient in the age group [50,70) has a higher survival probability than a patient in the group [70,90), which is quite plausible.

Figure 3: The Estimated Survival Curve for the two different Age Groups

The cumulative hazard function, $H(t)$, of the two age groups is given below by Figure 4.

As the above figure 4 suggests, the cumulative hazard for patients in the age group [70,90) is more than patients belonging to [50,70). We see that the cumulative hazard is the same for two age groups, almost up to $t = 1000$ days. After that, the cumulative hazard is exponentially increasing for the age
group [70,90). However, for the age group [50,70), the cumulative hazard has an increasing pattern up to \( t = 5800 \) days approximately. After that, the graph has a steady pattern.

The following Table 1 illustrates the count of each category of all the risk factors after stratification.

**Table 1:** Table Showing the Count of Different Categories of Risk Factors

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>135</td>
</tr>
<tr>
<td>Regional</td>
<td>178</td>
</tr>
<tr>
<td>Distant</td>
<td>364</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>333</td>
</tr>
<tr>
<td>No</td>
<td>344</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>168</td>
</tr>
<tr>
<td>No</td>
<td>509</td>
</tr>
<tr>
<td>Relatives</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>650</td>
</tr>
<tr>
<td>No</td>
<td>27</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>83</td>
</tr>
<tr>
<td>No</td>
<td>594</td>
</tr>
<tr>
<td>Heart attack</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>84</td>
</tr>
<tr>
<td>No</td>
<td>593</td>
</tr>
<tr>
<td>Emphysema</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19</td>
</tr>
<tr>
<td>No</td>
<td>658</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>388</td>
</tr>
<tr>
<td>Female</td>
<td>289</td>
</tr>
<tr>
<td>BMI</td>
<td>677</td>
</tr>
<tr>
<td>Cigarette Years</td>
<td>677</td>
</tr>
<tr>
<td>Diverticulosis</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>636</td>
</tr>
<tr>
<td>Smoke</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>404</td>
</tr>
<tr>
<td>No</td>
<td>273</td>
</tr>
<tr>
<td>Gallbladder</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>98</td>
</tr>
<tr>
<td>No</td>
<td>579</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>256</td>
</tr>
<tr>
<td>No</td>
<td>421</td>
</tr>
</tbody>
</table>

The step-wise procedure produced *seven* out of fourteen significant risk factors and *ten* two-way interaction terms. There were some risk factors that did not contribute to the hazard individually, but, interacting with other risk factors, their effect was significant. Thus, we added those risk factors in our proposed model. That is why there are thirteen individual risk factors and ten interactions in the model (11). In the following model (11), we denote "Y" to indicate yes of a specific answer of a risk factor. That is, the specific category possesses the characteristic. For example, to answer the question "does the patient ever have diabetes?" the individual answers "yes." To describe any particular category of the risk factor *stage*, we use \( L, R, \) and \( D \) which are the first letters of Localized, Regional, and Distant. To describe male and female category of the variable *Sex*, we use the letters \( M \) and \( F \), respectively. The most parsimonious model that we found after removing the insignificant (p-value > 0.05) term from the model is given as follows:
We can express the Cox-PH model (11) in the form of the survival function,
\[
S(t) = \exp \left( \sum_{i=1}^{p} \hat{\beta}_j X_{ij} + \sum_{j \neq k} \hat{\eta}_{jk} X_{ij} X_{ik} \right)
\]
\[
\ln \left[ \frac{h_i(t)}{\lambda_0(t)} \right] = \left\{ \begin{array}{l}
0.3X_{2R} + 0.5X_{2D} - 0.53X_{3Y} \\
+0.61X_{4Y} - 0.37X_{15Y} + 0.87X_{6Y} \\
-0.6X_{5Y} - 0.7X_{8Y} \\
-0.35X_{9F} + 0.0037X_{11} - 0.51X_{12Y} + 0.15X_{13Y} \\
+0.28X_{14Y} - 0.56X_{4Y}X_{13Y} + 0.41X_{3Y}X_{9F} \\
+0.63X_{3Y}X_{15Y} + 0.01X_{2R}X_{11} + 0.68X_{12Y}X_{9F} \\
+0.32X_{15Y}X_{9F} - 0.47X_{15Y}X_{14Y} \\
-0.52X_{2R}X_{4Y} + 2.18X_{2R}X_{8Y} + 0.8X_{15Y}X_{12Y}
\end{array} \right.
\]

Thus, the proposed statistical model consists of thirteen individual risk factors and ten interactions that contributes to the hazard.

a) Estimating the Survival Function

The above equation (10) can be written as:
\[
h_i(t; X_{ij}, X_{ij}X_{ik}) = h_{0s}(t) \exp \left[ \sum_{j=1}^{p} \hat{\beta}_j X_{ij} + \sum_{j \neq k} \hat{\eta}_{jk} X_{ij} X_{ik} \right], j \neq k
\]

We can express the Cox-PH model (11) in the form of the survival function, \( S(t) \), by employing equation (5) from Section 3. Thus, the survival function of the Cox-PH model can be expressed as:
\[
\hat{S}_i(t; X_{ij}, X_{ij}X_{ik}) = \exp \left[ - \int_0^t h_i(t; X_{ij}, X_{ij}X_{ik}) dt \right]
\]
\[
= \exp \left[ - \int_0^t h_{0s}(t) \exp \left[ \sum_{j=1}^{p} \hat{\beta}_j X_{ij} + \sum_{j \neq k} \hat{\eta}_{jk} X_{ij} X_{ik} \right] dt \right]
\]
\[
= \exp \left[ \exp \left[ \sum_{j=1}^{p} \hat{\beta}_j X_{ij} + \sum_{j \neq k} \hat{\eta}_{jk} X_{ij} X_{ik} \right] \left( - \int_0^t h_{0s}(t) dt \right) \right]
\]
\[
= \exp \left[ - \int_0^t h_{0s}(t) dt \right] \left[ \sum_{j=1}^{p} \hat{\beta}_j X_{ij} + \sum_{j \neq k} \hat{\eta}_{jk} X_{ij} X_{ik} \right]
\]
\[
= \left[ S_{0s}(t) \right] \left[ \sum_{j=1}^{p} \hat{\beta}_j X_{ij} + \sum_{j \neq k} \hat{\eta}_{jk} X_{ij} X_{ik} \right]
\]

where \( \hat{S}_{is}(t; X_{ij}, X_{ij}X_{ik}) \) is the survival function at time \( t \) for \( i^{th} \) individual and \( s^{th} \), \((s = 1, 2)\) stratum. \( S_{0s}(t) \) is the baseline survivor function for each stratum \( s = 1, 2 \). After the estimation of \( \hat{\beta} \) and \( \hat{\eta}_{jk} \) by partial likelihood (16), \( S_{0s}(t) \) can be estimated by a non-parametric maximum likelihood method (17). The co-efficient estimates of parameters \( \hat{\beta} \) and \( \hat{\eta}_{jk} \) are given in the third column of Table 2.

Table 2 below displays the estimates of the model coefficients/parameters, their hazard ratios (HR) \( (exp(\hat{\beta})) \), standard error of coefficients, statistical significance, and 95% confidence interval. We proceed to rank the significant contributing risk factors and their significant interactions based on the prognostic effect on the survival times of patients diagnosed with pancreatic cancer using the hazard
Survival Analysis for Pancreatic Cancer Patients using Cox-Proportional Hazard (CPH) Model

Year 2021

Global Journal of Medical Research
Volume XXI Issue III Version I

© 2021 Global Journals

Table 2: Ranking of the Significant Contributing Risk Factors and Interactions Based on Prognostic Effect to the Survival Time using the Hazard Ratios

<table>
<thead>
<tr>
<th>Rank</th>
<th>Risk Factors</th>
<th>coeff(β)</th>
<th>HR [exp(β)]</th>
<th>[S.E.(β)]</th>
<th>Lower 95%</th>
<th>Upper 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>X_{2R}X_{8Y}</td>
<td>2.18</td>
<td>8.84</td>
<td>.96</td>
<td>1.32</td>
<td>59.1</td>
</tr>
<tr>
<td>2</td>
<td>X_{6Y}</td>
<td>.87</td>
<td>2.39</td>
<td>.33</td>
<td>1.2</td>
<td>4.6</td>
</tr>
<tr>
<td>3</td>
<td>X_{15Y}X_{12Y}</td>
<td>.8</td>
<td>2.28</td>
<td>.38</td>
<td>1.07</td>
<td>4.87</td>
</tr>
<tr>
<td>4</td>
<td>X_{12Y}X_{9F}</td>
<td>.68</td>
<td>1.98</td>
<td>.39</td>
<td>.92</td>
<td>4.25</td>
</tr>
<tr>
<td>5</td>
<td>X_{4Y}</td>
<td>.61</td>
<td>1.834</td>
<td>.25</td>
<td>1.27</td>
<td>2.62</td>
</tr>
<tr>
<td>6</td>
<td>X_{3Y}X_{15Y}</td>
<td>.6</td>
<td>1.831</td>
<td>.18</td>
<td>1.11</td>
<td>3.02</td>
</tr>
<tr>
<td>7</td>
<td>X_{2D}</td>
<td>.5</td>
<td>1.63</td>
<td>.17</td>
<td>1.16</td>
<td>2.3</td>
</tr>
<tr>
<td>8</td>
<td>X_{3Y}X_{9F}</td>
<td>.41</td>
<td>1.5</td>
<td>.18</td>
<td>1.06</td>
<td>2.13</td>
</tr>
<tr>
<td>9</td>
<td>X_{15Y}X_{9F}</td>
<td>.32</td>
<td>1.37</td>
<td>.18</td>
<td>.96</td>
<td>1.96</td>
</tr>
<tr>
<td>10</td>
<td>X_{2R}X_{11}</td>
<td>0.01</td>
<td>1.01</td>
<td>.007</td>
<td>.99</td>
<td>1.05</td>
</tr>
<tr>
<td>11</td>
<td>X_{9F}</td>
<td>-.35</td>
<td>.7</td>
<td>.13</td>
<td>.54</td>
<td>.91</td>
</tr>
<tr>
<td>12</td>
<td>X_{15Y}</td>
<td>-.37</td>
<td>.69</td>
<td>.16</td>
<td>.5</td>
<td>.95</td>
</tr>
<tr>
<td>13</td>
<td>X_{15Y}X_{14Y}</td>
<td>-.47</td>
<td>.63</td>
<td>.26</td>
<td>.42</td>
<td>.94</td>
</tr>
<tr>
<td>14</td>
<td>X_{13Y}X_{4Y}</td>
<td>-.46</td>
<td>.63</td>
<td>.2</td>
<td>.42</td>
<td>.94</td>
</tr>
<tr>
<td>15</td>
<td>X_{3Y}</td>
<td>-.53</td>
<td>.6</td>
<td>.13</td>
<td>.45</td>
<td>.77</td>
</tr>
<tr>
<td>16</td>
<td>X_{2R}X_{4Y}</td>
<td>-.52</td>
<td>.59</td>
<td>.3</td>
<td>.33</td>
<td>1.05</td>
</tr>
<tr>
<td>17</td>
<td>X_{5Y}</td>
<td>-.6</td>
<td>.55</td>
<td>.2</td>
<td>.35</td>
<td>.84</td>
</tr>
</tbody>
</table>

The above Table 2 describes different information, including the hazard ratio of all seven significant risk factors and all ten significant interactions used in the model. A positive estimated coefficient/weight ($\beta > 0$) implies higher hazard rate, and thus a bad prognostic factor. on the contrary, a negative estimated coefficient/weight ($\beta < 0$) implies a lower hazard rate, and thus a good prognostic factor. For example, $\hat{\beta}_{9F} = -0.35$ from Table 2, implies females are good prognostic of the survival time of pancreatic cancer; thus, females have a lower risk of death (higher survival rates) of cancer than males. The $exp(\hat{\beta})$ is the hazard ratio (HR). Thus, $exp(-0.35) = .7 < 1$ for gender female means being a female has a reduced risk of dying with pancreatic cancer than being a male. The ranking of the significant risk factors from Table 2, based on the HR, shows that the interaction between cancer stage (Regional) and patient having Emphysema ($X_{2R}X_{8Y}$) is the highest prognostic factor to the survival of pancreatic cancer, followed by patients having diabetes ($X_{6Y}$), and Relatives who have pancreatic cancer ($X_{5Y}$) is the least prognostic factor. We also provide the 95% confidence interval of the hazard ratios (HR) corresponding to the risk factors; that is,

$$P[UCL \leq HR \leq LCL] \geq 95\%$$

where $UCL$ and $LCL$ are the upper and lower confidence limits and we are at least 95% confident that the hazard ratios will fall into the limits. The following Table 3 provides the three popular global tests of significance which our model is based on. As, the following table shows, our proposed model (11) is highly significant based on all the three statistical tests.
V. Assumptions of Cox PH Model and Validation of the Proposed Model

In order to apply the CPH model, we must verify that the following three key assumptions are satisfied, prior to its implementation. Failure to satisfy these assumptions will bring about inaccurate decisions about the subject matter.

1. Proportional hazard (PH) assumption: The proportional hazard assumption of the Cox model can be validated depending on formal statistical tests. A non-statistical significance of all risk factors along with the interactions in the model with the global test is an evidence that the PH assumption is well-grounded. Another way to verify the PH assumption is by investigating the plot of scaled Schoenfeld residuals against the transformed time. The Schoenfeld residuals are independent of time; a non-random pattern against time is evidence of a violation of the PH assumption. We calculate the Schoenfeld residuals for each of the risk factors and all interactions.

The data consists of times $T_1, T_2, \ldots, T_n$ which are either observed survival times or censored times with censoring indicators $\delta_1, \delta_2, \ldots, \delta_n$. $\delta_i = 1$ implies $T_i$ is observed, and $\delta_i = 0$ implies $T_i$ is censored. Suppose there are $p$ fixed covariates/risk factors $Z_1, Z_2, \ldots, Z_n$ and $R_i$ be the risk set at time $T_i$ denoted as $R_i = \{ j : T_j \geq T_i \}$. Given the setup, the partial likelihood, proposed by Cox (1975) is defined by:

$$
L(\beta) = \prod_{i=1}^n \delta_i \left[ \beta^T Z_i - \log \left( \sum_{j \in R_i} \exp(\beta^T Z_j) \right) \right].
$$

(14)

Let $\hat{\beta}$ be the usual estimator of $\beta$ that minimizes $L(\beta)$ in (13). Also, let $t_{(i)}$ be the $i^{th}$ ordered observed survival time and $Z_{(i)}$ and $R_i$ the corresponding covariate vector and risk set. Then Schoenfeld’s residuals are defined as follows:

$$
\hat{r}_i = Z_{(i)} - \frac{\sum_{j \in R_i} Z_j \exp(\hat{\beta}^T Z_j)}{\sum_{j \in R_i} \exp(\hat{\beta}^T Z_j)}.
$$

(15)

The following Figures 5 and 6 illustrate the plot of the scaled Schoenfeld residual against time for all risk factors and interaction terms used in the model (11), respectively. It shows that there is no pattern as a function of time. Thus, the residuals are randomly scattered with no systematic departures from the horizontal fitted smoothing spline deep line (that is, the residuals are independent of times).
A formal test for the PH assumption is given in Table 4. The covariates and the global test are non-statistically significant given by the large p-values. This is a further justification of the validity of the PH assumption for our proposed model. We have included all fourteen risk factors and ten interaction terms in the table. The number of terms in Table 4 is greater than Table 2 since we have included all of the fourteen individual risk factors used in our analysis in Table 4.
2. **Linear Functional Form of continuous Risk Factors**: Often, many researchers assume that the continuous risk factors in the Cox PH model have a linear form. However, one should verify this assumption before implementation of the model. Representing the Martingale residuals against continuous covariates is a graphical form, is a common approach to identify the nonlinearity or, in other words, to assess the functional form of a covariate. For a given continuous covariate, the plot patterns may suggest that the variable is not properly fit. Nonlinearity is not a problem for categorical risk factors. So we only investigate plots of martingale residuals against the only continuous covariate \(X_{11}\). Sometimes, these plots can help select the appropriate functional forms of the risk factors in the Cox model. The *martingale residual*, proposed by Therneau and Grambsch (21) is given by,

\[
\hat{M}_i = \delta_i - \hat{\Gamma}_0(t_i)exp\left[\sum_{j=1}^{p} \hat{\beta}_{ij}X_{ij} + \sum_{j \neq k} \hat{\eta}_{jk}X_{ij}X_{ik}\right], \ j \neq k.
\]

where \(\delta_i\) denotes the event indicator for \(i^{th}\) observation, \(\hat{\Gamma}_0(t_i)\) is the estimated cumulative hazard at the final follow-up time for the \(i^{th}\) observation. Martingale residuals, \(\hat{M}_i\), have a skewed distribution. We have, \(\hat{M}_i = 1\) for for maximum possible values and \(\hat{M}_i = -\infty\)
for minimum possible values. Positive values of $\hat{M}_i$ indicate those patients expired too early compared to expected survival times. On the contrary, negative values of $M_i$ correspond to patients who were alive for a long time.

As shown in the Figure 7, the data points are fairly linear for almost all points except around $X_{11} = 10$. The continuous covariate $X_{11}$ is the number of cigarette smoking years of an individual patient. There are several patients who did not smoke at all (indicated by the points around zero). If we omit these observations, the pattern of the graph is fairly linear and increasing.

3. **Testing influential observations and Outliers**: Often influential observations can cause problems with modeling results. In order to check the influential observations, we visualized the dfbeta values. The dfbeta values estimates the influence of the $i^{th}$ patient observation on the regression coefficients $\beta_j$. A high value of dfbeta must be investigated carefully. Another method for checking influential observations is by assessing the deviance residuals (symmetric/normalized transformation of the Martingale residuals) plot. The deviance residual is defined by

$$d_i = \sin(\hat{M}_i) \sqrt{2 \sqrt{-\hat{M}_i - \delta_i \log(\delta_i - \hat{M}_i)}}.$$ 

In the above equation, $\hat{M}_i$ implies $d_i = 0$. The square root shrinks the large negative martingale residuals, while the logarithm transformation expands those residuals that are close to zero. The distribution of the residuals must approximately be symmetrical around mean zero and standard deviation of one. A very large/small/distant deviance residual values indicate influential observations or outliers. Figure 8 below implies that none of the observations is exceedingly influential individually, on average.
The following Figure 9 plots the deviance residual and the residual pattern looks fairly symmetrical around zero. The mean deviance residual for our model is .2 which is very small.

VI. Results and Discussions

Given the risk posed by pancreatic cancer in the past few years, it is imperative to investigate the clinical diagnosis and enhance the therapeutic/treatment strategy of pancreatic cancer. The primary treatment for most types of pancreatic cancer is chemotherapy. Sometimes, with chemotherapy, specific therapy drugs are used. Usually, surgery and radiation therapy do not fall under crucial treatments.
for pancreatic cancer, but they might be used in exceptional circumstances. Also, the treatment approach for children with pancreatic cancer can be slightly different from that used for adults. Several research approaches and statistical methodologies (23) (24) have been developed to cure pancreatic cancer patients and boost their survival times. Chakraborty & Tsokos (to be published) performed data-driven research on pancreatic cancer patients by performing parametric analysis to improve the survival probabilities of patients of different cancer stages. In the present study, we initially investigated if there exists any statistically significant difference between the true mean survival times of the male and female pancreatic cancer patients using the Wilcoxon two-sample rank-sum test. The p-value (.47 > .05) of the test result suggests that there is no evidence of a significant difference between the true mean survival times of the males and the females. Hence, we proceed to perform to develop the Cox-PH (CPH) model with the combined information of male and female patients. While developing the CPH model, it is very important to justify the model assumptions. In the preliminary analysis, we found that all of the risk factors except age ($X_1$) did not satisfy the proportional hazard assumption. Thus, we introduced stratification in our model by dividing the covariate age into two groups. By doing stratification, we obtained more valid estimates of the other covariates, and the proportional hazard assumption was satisfied for all risk factors, including age. Performing stratification, we restrict the effect of the covariates to be the same for each stratum. Our final developed Cox-PH model given by equation (11) identified all the significant risk factors along with all the significant interaction terms as contributing to the hazard. After building our model, we proceed to rank all significant individual risk factors and all possible significant interactions according to the hazard ratio, as shown in Table 2. From Table 2, we observe that $X_{6Y}$ (patients having diabetes), $X_{4Y}$ (patients taking ibuprofen regularly), $X_{2D}$ (patients who are in stage distant (Cancer has spread to distant parts of the body)), $X_{9F}$ (sex), and $X_{15Y}$ (hypertension) are the most contributing risk factors individually to the survival of patients with a hazard ratio (HR) of 2.39, 1.83, 1.63, .7, and .7, respectively. For the risk factor $X_{6Y}$, HR = 2.39 indicates a strong association between the patients having diabetes and increased risk of death due to pancreatic cancer. Keeping the other covariates constant, being a diabetic patient has a 2.39-fold increase in the hazard of death; that is, 2.39-fold increased risk (or decreased survival). It is important to note that according to the American Cancer Society, one of the main risk factors of pancreatic cancer is diabetes which is supported by our study. Also, we have found that those who take ibuprofen regularly have an increased risk of 1.83-fold than those who do not take the medication on a regular basis. Also, being a female has approximately 30% less hazard than a male patient. Among the most significant interactions we have $X_{2R}X_{8Y}$, $X_{15Y}X_{12Y}$, $X_{12Y}X_{9F}$, $X_{3Y}X_{15Y}$, $X_{3Y}X_{9F}$, $X_{15Y}X_{9F}$, and $X_{2R}X_{11}$ with hazard ratio 8.84, 2.28, 1.98, 1.83, 1.5, 1.37, and 1.01 respectively. The most contributing risk factor is an interaction term ($X_{2R}X_{8Y}$) (patients with emphysema and cancer stage regional with HR = 8.84). However, they do not contribute significantly to survival. We see that $X_{15Y}$ (hypertension) has a lower risk of survival (HR = .79). However, interacting with $X_{12Y}$ (diverticulosis), it has a hazard ratio of 2.28. Also, interacting with $X_{3Y}$ (person who uses Aspirin Regularly), it has a hazard ratio of 2.28. It is also important to note that $X_{3Y}$ individually has lower risk (better survival) with HR = .6. Although $X_{12Y}$ (diverticulosis) and $X_{9F}$ (female) has a hazard ratio less than one, their combined effect remains significant with HR = 1.98.

VII. CONCLUSION

In this study, we have estimated the survival probabilities of patients diagnosed with pancreatic cancer using the semi-parametric Cox proportional hazard (CPH) model. We believe the proposed Cox-PH model given by equation (11) gives an accurate estimate of the survival probability of patients diagnosed with pancreatic cancer. The stratification of the age produced more reliable estimates of the risk factor included in the CPH model. We identified seven significant risk factors and ten significant interaction terms as contributing to the survival probability of patients diagnosed with pancreatic cancer.
cancer, as described in Table 2. We also ranked those risk factors and their interactions based on the hazard ratio. There have not enough studies been done in the literature that incorporates the significant interaction effect of two risk factors. Interaction effects play a major role as a prognostic factor in addition to the individual risk factors in the CPH model. We found some of the risk factors used in our study individually have hazard less than one, but by combining with some other risk factor, the hazard was more than 1.5, and the combined effect was significant. Our final proposed Cox-PH model is of very high quality, robust, and efficient, given by the fact that it satisfies all the major assumptions described in Section 5. The stepwise model selection procedure was utilized to carefully assess and select the risk factors and the interaction term based on their statistical significance to the survival probability. Depending on the survival analysis of the survival times based on the CPH model of the pancreatic cancer patients, we recommend the following.

1. Besides the survival time of patients, if any additional details regarding some of the potential risk factors are known, then use of the Cox proportional hazard (CPH) model can reflect a better picture of covariate effect on survival via hazard ratio.

2. Before implementing the developed CPH model, one should be careful about the fact that the CPH model assumptions are satisfied. In our present analysis, we justified the key assumptions of the CPH model.

3. The significant two-way interaction effects of the risk factors in the CPH model should not be excluded because they can significantly influence the prediction accuracy of the model and survival rate of pancreatic cancer patients, which might lead to serious clinical and therapeutic/treatment issues.

4. The ranking of the individual and interacting risk factors can be wisely used in pancreatic cancer research to improve the treatment options.

Acknowledgement

The authors are thankful to the National Cancer Institute (NIH) for making the data available.

Funding
Not Applicable

Ethics approval and consent to participate
Not Applicable

Competing interests
There are no competing interests to declare.

References Références Referencias


MEMBERSHIPS

FELLOWS/ASSOCIATES OF MEDICAL RESEARCH COUNCIL

FMRC/AMRC MEMBERSHIPS

INTRODUCTION

FMRC/AMRC is the most prestigious membership of Global Journals accredited by Open Association of Research Society, U.S.A (OARS). The credentials of Fellow and Associate designations signify that the researcher has gained the knowledge of the fundamental and high-level concepts, and is a subject matter expert, proficient in an expertise course covering the professional code of conduct, and follows recognized standards of practice. The credentials are designated only to the researchers, scientists, and professionals that have been selected by a rigorous process by our Editorial Board and Management Board.

Associates of FMRC/AMRC are scientists and researchers from around the world are working on projects/researches that have huge potentials. Members support Global Journals’ mission to advance technology for humanity and the profession.

FMRC

FELLOW OF MEDICAL RESEARCH COUNCIL

FELLOW OF MEDICAL RESEARCH COUNCIL is the most prestigious membership of Global Journals. It is an award and membership granted to individuals that the Open Association of Research Society judges to have made a 'substantial contribution to the improvement of computer science, technology, and electronics engineering.

The primary objective is to recognize the leaders in research and scientific fields of the current era with a global perspective and to create a channel between them and other researchers for better exposure and knowledge sharing. Members are most eminent scientists, engineers, and technologists from all across the world. Fellows are elected for life through a peer review process on the basis of excellence in the respective domain. There is no limit on the number of new nominations made in any year. Each year, the Open Association of Research Society elect up to 12 new Fellow Members.
**Benefit**

**To the institution**

**Get Letter of Appreciation**
Global Journals sends a letter of appreciation of author to the Dean or CEO of the University or Company of which author is a part, signed by editor in chief or chief author.

**Exclusive Network**

**Get Access to a Closed Network**
A FMRC member gets access to a closed network of Tier 1 researchers and scientists with direct communication channel through our website. Fellows can reach out to other members or researchers directly. They should also be open to reaching out by other.

**Certificate**

**Certificate, LoR and Laser-Momento**
Fellows receive a printed copy of a certificate signed by our Chief Author that may be used for academic purposes and a personal recommendation letter to the dean of member's university.

**Designation**

**Get Honored Title of Membership**
Fellows can use the honored title of membership. The "FMRC" is an honored title which is accorded to a person’s name viz. Dr. John E. Hall, Ph.D., FMRC or William Walldroff, M.S., FMRC.

**Recognition on the Platform**

**Better Visibility and Citation**
All the Fellow members of FMRC get a badge of “Leading Member of Global Journals” on the Research Community that distinguishes them from others. Additionally, the profile is also partially maintained by our team for better visibility and citation. All fellows get a dedicated page on the website with their biography.
FUTURE WORK
GET DISCOUNTS ON THE FUTURE PUBLICATIONS
Fellows receive discounts on the future publications with Global Journals up to 60%. Through our recommendation programs, members also receive discounts on publications made with OARS affiliated organizations.

GJ INTERNAL ACCOUNT
UNLIMITED FORWARD OF EMAILS
Fellows get secure and fast GJ work emails with unlimited storage of emails that they may use them as their primary email. For example, john [AT] globaljournals [DOT] org.

PREMIUM TOOLS
ACCESS TO ALL THE PREMIUM TOOLS
To take future researches to the zenith, fellows receive access to all the premium tools that Global Journals have to offer along with the partnership with some of the best marketing leading tools out there.

CONFERENCES & EVENTS
ORGANIZE SEMINAR/CONFERENCE
Fellows are authorized to organize symposium/seminar/conference on behalf of Global Journal Incorporation (USA). They can also participate in the same organized by another institution as representative of Global Journal. In both the cases, it is mandatory for him to discuss with us and obtain our consent. Additionally, they get free research conferences (and others) alerts.

EARLY INVITATIONS
EARLY INVITATIONS TO ALL THE SYMPOSIUMS, SEMINARS, CONFERENCES
All fellows receive the early invitations to all the symposiums, seminars, conferences and webinars hosted by Global Journals in their subject.

© Copyright by Global Journals | Guidelines Handbook
PUBLISHING ARTICLES & BOOKS

EARN 60% OF SALES PROCEEDS

Fellows can publish articles (limited) without any fees. Also, they can earn up to 70% of sales proceeds from the sale of reference/review books/literature/publishing of research paper. The FMRC member can decide its price and we can help in making the right decision.

reviewers

GET A REMUNERATION OF 15% OF AUTHOR FEES

Fellow members are eligible to join as a paid peer reviewer at Global Journals Incorporation (USA) and can get a remuneration of 15% of author fees, taken from the author of a respective paper.

access to editorial board

BECOME A MEMBER OF THE EDITORIAL BOARD

Fellows and Associates may join as a member of the Editorial Board of Global Journals Incorporation (USA) after successful completion of three years as Fellow and as Peer Reviewer.

And Much More

Get access to scientific museums and observatories across the globe

All members get access to 5 selected scientific museums and observatories across the globe. All researches published with Global Journals will be kept under deep archival facilities across regions for future protections and disaster recovery. They get 10 GB free secure cloud access for storing research files.
The primary objective is to recognize the leaders in research and scientific fields of the current era with a global perspective and to create a channel between them and other researchers for better exposure and knowledge sharing. Members are most eminent scientists, engineers, and technologists from all across the world. Associate membership can later be promoted to Fellow Membership. Associates are elected for life through a peer review process on the basis of excellence in the respective domain. There is no limit on the number of new nominations made in any year. Each year, the Open Association of Research Society elect up to 12 new Associate Members.
**Benefit**

**To the Institution**

**Get Letter of Appreciation**

Global Journals sends a letter of appreciation of author to the Dean or CEO of the University or Company of which author is a part, signed by editor in chief or chief author.

**Exclusive Network**

**Get Access to a Closed Network**

A AMRC member gets access to a closed network of Tier 2 researchers and scientists with direct communication channel through our website. Associates can reach out to other members or researchers directly. They should also be open to reaching out by other.

**Certificate**

**Certificate, LoR and Laser-Momento**

Associates receive a printed copy of a certificate signed by our Chief Author that may be used for academic purposes and a personal recommendation letter to the dean of member's university.

**Designation**

**Get Honored Title of Membership**

Associates can use the honored title of membership. The "AMRC" is an honored title which is accorded to a person’s name viz. Dr. John E. Hall, Ph.D., AMRC or William Walldroff, M.S., AMRC.

**Recognition on the Platform**

**Better Visibility and Citation**

All the Associate members of AMRC get a badge of “Leading Member of Global Journals” on the Research Community that distinguishes them from others. Additionally, the profile is also partially maintained by our team for better visibility and citation.

© Copyright by Global Journals | Guidelines Handbook
**Future Work**

**Get discounts on the future publications**
Associates receive discounts on future publications with Global Journals up to 30%. Through our recommendation programs, members also receive discounts on publications made with OARS affiliated organizations.

---

**GJ Account**

**Unlimited forward of Emails**
Associates get secure and fast GJ work emails with 5GB forward of emails that they may use them as their primary email. For example, john[@]globaljournals[DOT]org.

---

**Premium Tools**

**Access to all the premium tools**
To take future researches to the zenith, fellows receive access to almost all the premium tools that Global Journals have to offer along with the partnership with some of the best marketing leading tools out there.

---

**Conferences & Events**

**Organize seminar/conference**
Associates are authorized to organize symposium/seminar/conference on behalf of Global Journal Incorporation (USA). They can also participate in the same organized by another institution as representative of Global Journal. In both the cases, it is mandatory for him to discuss with us and obtain our consent. Additionally, they get free research conferences (and others) alerts.

---

**Early Invitations**

**Early invitations to all the symposiums, seminars, conferences**
All associates receive the early invitations to all the symposiums, seminars, conferences and webinars hosted by Global Journals in their subject.
PUBLISHING ARTICLES & BOOKS

EARN 60% OF SALES PROCEEDS

Associates can publish articles (limited) without any fees. Also, they can earn up to 30-40% of sales proceeds from the sale of reference/review books/literature/publishing of research paper.

REVIEWERS

GET A REMUNERATION OF 15% OF AUTHOR FEES

Associate members are eligible to join as a paid peer reviewer at Global Journals Incorporation (USA) and can get a remuneration of 15% of author fees, taken from the author of a respective paper.

AND MUCH MORE

GET ACCESS TO SCIENTIFIC MUSEUMS AND OBSERVATORIES ACROSS THE GLOBE

All members get access to 2 selected scientific museums and observatories across the globe. All researches published with Global Journals will be kept under deep archival facilities across regions for future protections and disaster recovery. They get 5 GB free secure cloud access for storing research files.
<table>
<thead>
<tr>
<th>ASSOCIATE</th>
<th>FELLOW</th>
<th>RESEARCH GROUP</th>
<th>BASIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>$4800 lifetime designation</td>
<td>$6800 lifetime designation</td>
<td>$12500.00 organizational</td>
<td>APC per article</td>
</tr>
<tr>
<td>Certificate, LoR and Momento</td>
<td>Certificate, LoR and Momento</td>
<td>Certificate, LoRs and Momentos</td>
<td>GJ Community Access</td>
</tr>
<tr>
<td>2 discounted publishing/year</td>
<td>Unlimited discounted</td>
<td>10 research contacts/day</td>
<td>1 GB Cloud Storage</td>
</tr>
<tr>
<td>Gradation of Research</td>
<td>publishing/year</td>
<td>1 GB Cloud Storage</td>
<td>GJ Community Access</td>
</tr>
<tr>
<td>10 research contacts/day</td>
<td>Gradation of Research</td>
<td>5 GB Cloud Storage</td>
<td></td>
</tr>
<tr>
<td>1 GB Cloud Storage</td>
<td>Unlimited research contacts/day</td>
<td>Online Presence Assistance</td>
<td></td>
</tr>
<tr>
<td>GJ Community Access</td>
<td>GJ Community Access</td>
<td>GJ Community Access</td>
<td></td>
</tr>
</tbody>
</table>

© Copyright by Global Journals | Guidelines Handbook
Preferred Author Guidelines

We accept the manuscript submissions in any standard (generic) format.

We typeset manuscripts using advanced typesetting tools like Adobe InDesign, CorelDraw, TeXnicCenter, and TeXStudio. We usually recommend authors submit their research using any standard format they are comfortable with, and let Global Journals do the rest.

Alternatively, you can download our basic template from https://globaljournals.org/Template

Authors should submit their complete paper/article, including text illustrations, graphics, conclusions, artwork, and tables. Authors who are not able to submit manuscript using the form above can email the manuscript department at submit@globaljournals.org or get in touch with chiefeditor@globaljournals.org if they wish to send the abstract before submission.

Before and during Submission

Authors must ensure the information provided during the submission of a paper is authentic. Please go through the following checklist before submitting:

1. Authors must go through the complete author guideline and understand and agree to Global Journals' ethics and code of conduct, along with author responsibilities.
2. Authors must accept the privacy policy, terms, and conditions of Global Journals.
3. Ensure corresponding author’s email address and postal address are accurate and reachable.
4. Manuscript to be submitted must include keywords, an abstract, a paper title, co-author(s’) names and details (email address, name, phone number, and institution), figures and illustrations in vector format including appropriate captions, tables, including titles and footnotes, a conclusion, results, acknowledgments and references.
5. Authors should submit paper in a ZIP archive if any supplementary files are required along with the paper.
6. Proper permissions must be acquired for the use of any copyrighted material.
7. Manuscript submitted must not have been submitted or published elsewhere and all authors must be aware of the submission.

Declaration of Conflicts of Interest

It is required for authors to declare all financial, institutional, and personal relationships with other individuals and organizations that could influence (bias) their research.

Policy on Plagiarism

Plagiarism is not acceptable in Global Journals submissions at all.

Plagiarized content will not be considered for publication. We reserve the right to inform authors’ institutions about plagiarism detected either before or after publication. If plagiarism is identified, we will follow COPE guidelines:

Authors are solely responsible for all the plagiarism that is found. The author must not fabricate, falsify or plagiarize existing research data. The following, if copied, will be considered plagiarism:

- Words (language)
- Ideas
- Findings
- Writings
- Diagrams
- Graphs
- Illustrations
- Lectures

© Copyright by Global Journals | Guidelines Handbook
Authorship Policies

Global Journals follows the definition of authorship set up by the Open Association of Research Society, USA. According to its guidelines, authorship criteria must be based on:

1. Substantial contributions to the conception and acquisition of data, analysis, and interpretation of findings.
2. Drafting the paper and revising it critically regarding important academic content.
3. Final approval of the version of the paper to be published.

Changes in Authorship

The corresponding author should mention the name and complete details of all co-authors during submission and in manuscript. We support addition, rearrangement, manipulation, and deletions in authors list till the early view publication of the journal. We expect that corresponding author will notify all co-authors of submission. We follow COPE guidelines for changes in authorship.

Copyright

During submission of the manuscript, the author is confirming an exclusive license agreement with Global Journals which gives Global Journals the authority to reproduce, reuse, and republish authors' research. We also believe in flexible copyright terms where copyright may remain with authors/employers/institutions as well. Contact your editor after acceptance to choose your copyright policy. You may follow this form for copyright transfers.

Appealing Decisions

Unless specified in the notification, the Editorial Board’s decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

Declaration of funding sources

Global Journals is in partnership with various universities, laboratories, and other institutions worldwide in the research domain. Authors are requested to disclose their source of funding during every stage of their research, such as making analysis, performing laboratory operations, computing data, and using institutional resources, from writing an article to its submission. This will also help authors to get reimbursements by requesting an open access publication letter from Global Journals and submitting to the respective funding source.

Preparing your Manuscript

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.
Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27” x 11”
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word “Abstract” in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references).

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper’s subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned un refereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.
It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

**Title**

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

**Author details**

The full postal address of any related author(s) must be specified.

**Abstract**

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

**Keywords**

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

**Numerical Methods**

Numerical methods used should be transparent and, where appropriate, supported by references.

**Abbreviations**

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

**Formulas and equations**

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

**Tables, Figures, and Figure Legends**

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.
Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Electronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.
6. **Bookmarks are useful:** When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. **Revise what you wrote:** When you write anything, always read it, summarize it, and then finalize it.

8. **Make every effort:** Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. **Produce good diagrams of your own:** Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. **Use proper verb tense:** Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. **Pick a good study spot:** Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. **Know what you know:** Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. **Use good grammar:** Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. **Arrangement of information:** Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. **Never start at the last minute:** Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. **Multitasking in research is not good:** Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. **Never copy others’ work:** Never copy others’ work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. **Go to seminars:** Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. **Refresh your mind after intervals:** Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.
20. **Think technically:** Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. **Adding unnecessary information:** Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn’t be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. **Report concluded results:** Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. **Upon conclusion:** Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium through which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

**Informal Guidelines of Research Paper Writing**

**Key points to remember:**

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

**Final points:**

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

**The introduction:** This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

**The discussion section:**

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

**General style:**

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

**To make a paper clear:** Adhere to recommended page limits.
Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.
The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study’s tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

*Materials may be reported in part of a section or else they may be recognized along with your measures.*

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that’s all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer’s interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

**What to keep away from:**

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.
Results:
The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:
- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:
- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:
As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:
If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:
The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."
Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

THE ADMINISTRATION RULES

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

Please read the following rules and regulations carefully before submitting your research paper to Global Journals Inc. to avoid rejection.

Segment draft and final research paper: You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.
**CRITERION FOR GRADING A RESEARCH PAPER (COMPILATION)
BY GLOBAL JOURNALS**

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

<table>
<thead>
<tr>
<th>Topics</th>
<th>Grades</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A-B</td>
</tr>
<tr>
<td>Abstract</td>
<td>Clear and concise with appropriate content, Correct format. 200 words or below</td>
</tr>
<tr>
<td></td>
<td>C-D</td>
</tr>
<tr>
<td></td>
<td>Unclear summary and no specific data, Incorrect form Above 200 words</td>
</tr>
<tr>
<td></td>
<td>E-F</td>
</tr>
<tr>
<td></td>
<td>No specific data with ambiguous information Above 250 words</td>
</tr>
<tr>
<td>Introduction</td>
<td>Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited</td>
</tr>
<tr>
<td></td>
<td>C-D</td>
</tr>
<tr>
<td></td>
<td>Unclear and confusing data, Appropriate format, grammar and spelling errors with unorganized matter</td>
</tr>
<tr>
<td></td>
<td>E-F</td>
</tr>
<tr>
<td></td>
<td>Out of place depth and content, Hazy format</td>
</tr>
<tr>
<td>Methods and Procedures</td>
<td>Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads</td>
</tr>
<tr>
<td>Result</td>
<td>C-D</td>
</tr>
<tr>
<td></td>
<td>Difficult to comprehend with embarrassed text, too much explanation but completed</td>
</tr>
<tr>
<td></td>
<td>E-F</td>
</tr>
<tr>
<td></td>
<td>Incorrect and unorganized structure with hazy meaning</td>
</tr>
<tr>
<td>Discussion</td>
<td>Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph, reference cited</td>
</tr>
<tr>
<td></td>
<td>C-D</td>
</tr>
<tr>
<td></td>
<td>Wordy, unclear conclusion, Spurious</td>
</tr>
<tr>
<td></td>
<td>E-F</td>
</tr>
<tr>
<td></td>
<td>Conclusion is not cited, unorganized, difficult to comprehend</td>
</tr>
<tr>
<td>References</td>
<td>Complete and correct format, well organized</td>
</tr>
<tr>
<td></td>
<td>C-D</td>
</tr>
<tr>
<td></td>
<td>Beside the point, Incomplete</td>
</tr>
<tr>
<td></td>
<td>E-F</td>
</tr>
<tr>
<td></td>
<td>Wrong format and structuring</td>
</tr>
</tbody>
</table>

© Copyright by Global Journals | Guidelines Handbook
INDEX

A
Adherent · 2
Assumption · 44, 52, 53, 54, 58
Authentic · 19

C
Causative · 28, 32, 34
Cessation · 32
Concordance · 10, 16
Cumulative · 40, 41, 42, 46, 48, 54

D
Deviance · 55, 56

E
Echogenic · 29
Eradication · 18
Explicate · 36

F
Feasible · 10, 16

I
Imputation · 38

M
Malignant · 1, 5, 14, 36
Manifested · 19

P
Palpable · 1
Parsimonious · 44, 48
Predominant · 18, 22, 24, 32
Prominent · 36

Q
Quadrant · 1

S
Surveillance · 36

V
Vulnerable · 46