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Gallbladder Stones in Children

Case Report and Review of Literature

Highlights

Cervical and Vaginal Specimens

Cox-Proportional Hazard (CPH) Model

Discovering Thoughts, Inventing Future

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Retroperitoneal Liposarcoma: A Case Report and Review of Literature

By Dr. Elize Isabella Wethmar

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*



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Retroperitoneal Liposarcoma: A Case Report and Review of Literature

Dr. Elize Isabella Wethmar

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 anasymptomatic 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 preperitoneum 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[1] ascending and descending colon, part of the duodenum, part of the pancreas and part of the liver[123]. 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.

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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[4].

b) 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[5].



Figure 1: Macroscopic appearance of the excised retroperitoneal liposarcoma

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[5]:

- 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 reproperitoneum[5].

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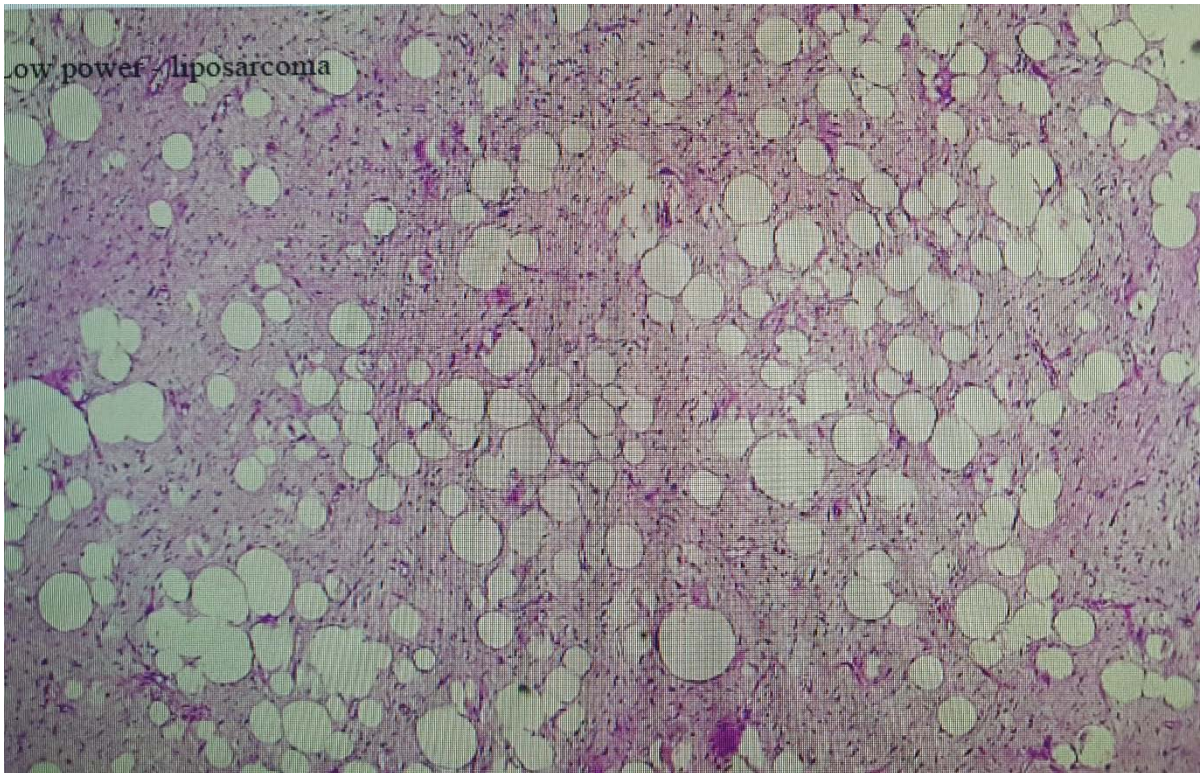


Figure 2: Low power microscopy view demonstrating a deifferentiated liposarcoma

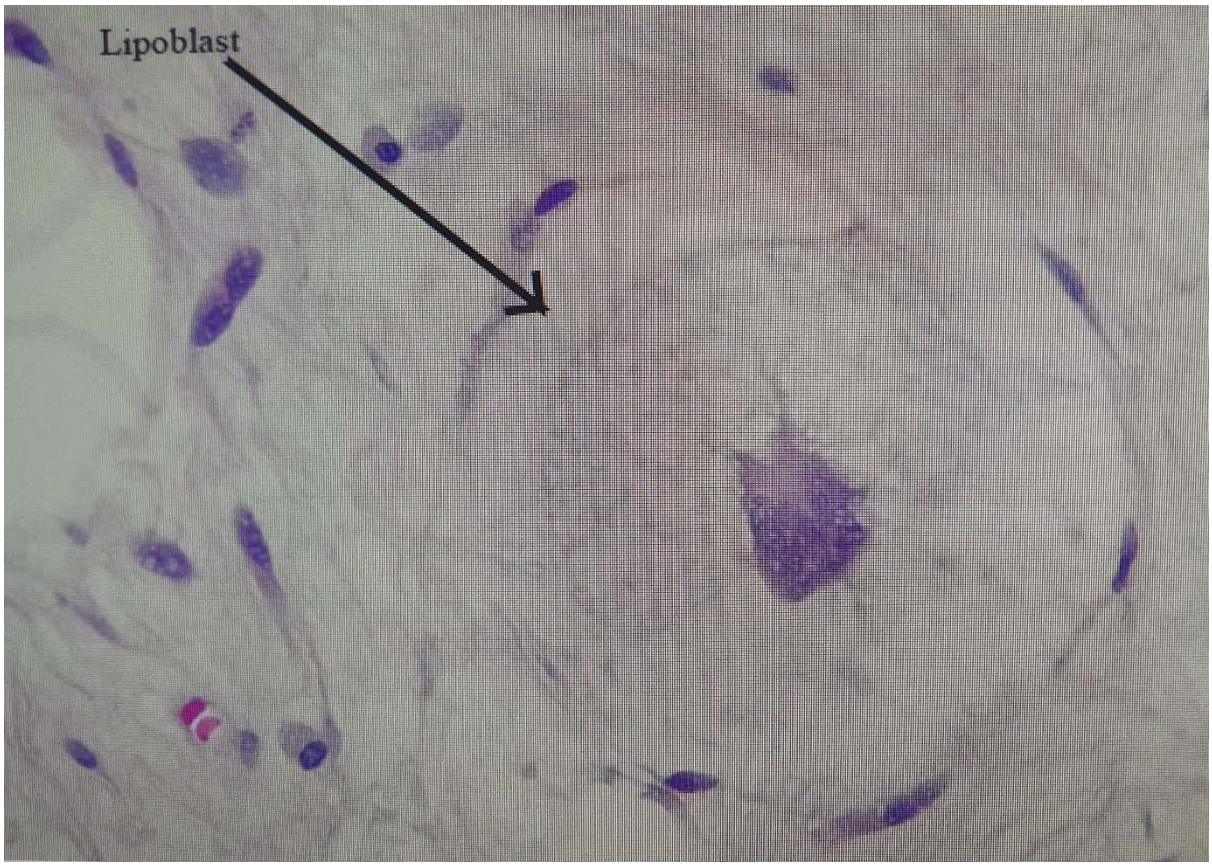


Figure 3: A microscopic view of a lipoblast, which may or may not be present in a liposarcoma

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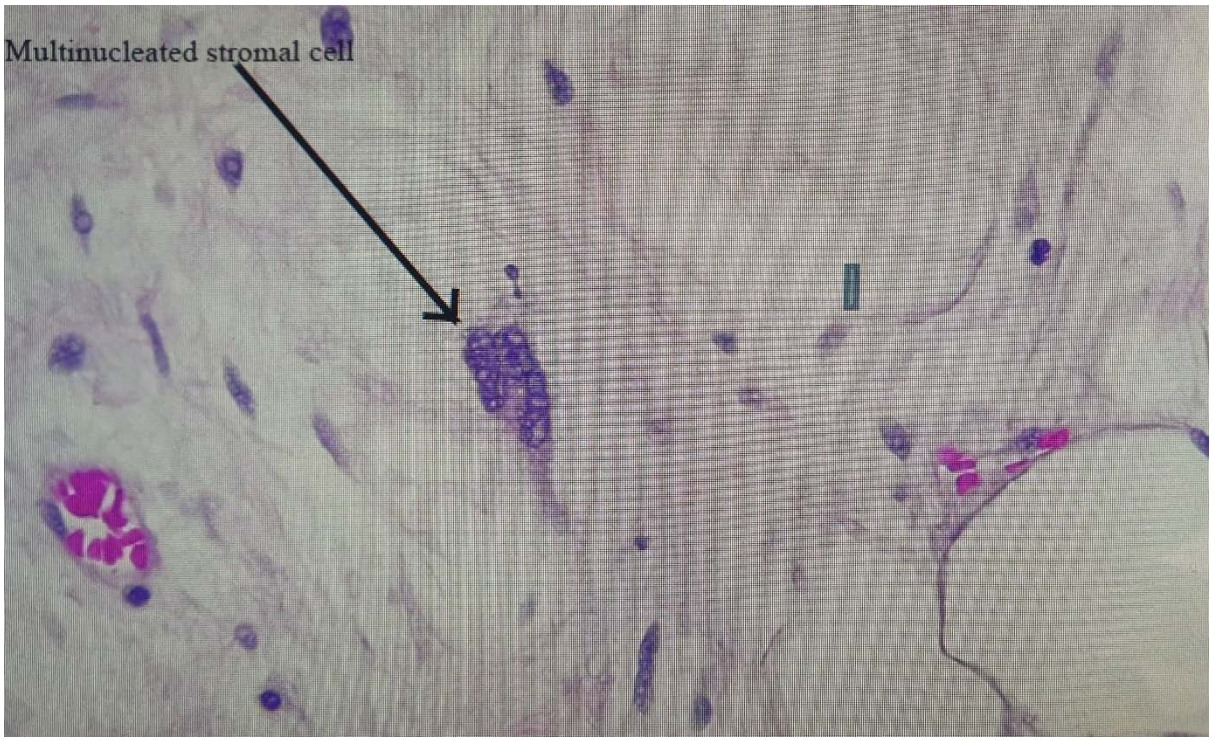


Figure 4: A multinucleated stromal cell which is present in a Sclerosing atypical lipomatous tumour during microscopy

Dedifferentiated liposarcoma can arise as a synchronous lesion in 90% of cases and as metachronous lesion in 10% of cases[6]. 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[5]. 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[7].

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[8].

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[9]. 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 HU9corresponding to fat[10]
- 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[10]. 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).

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Table 1: Positive signs indicating that a Retroperitoneal Tumour Arises from an Adjacent Organ[9]

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

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[9] and therefore aretroperitoneal purely fatty lesion should be considered a liposarcoma rather than a lipoma until proven otherwise with histological confirmation[1011]. 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[12].



Figure 5: Transverse CT-scan image demonstrating a liposarcoma

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Figure 6: Coronal CT scan image demonstrating the liposarcoma

d) Treatment options

i. *Surgery*

Surgery is the mainstay of treatment for non-metastatic retroperitoneal sarcoma[8]. 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[13]. 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[14].

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[15]. 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.

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iii. *Systemic therapy*

Chemotherapy has an established role in the palliative management of advanced or metastatic soft tissue sarcoma[8]. Active agents include the anthracyclines (doxorubicin and epirubicin) and the alkylating agent ifosfomide[16]. 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[8]. Well-differentiated and dedifferentiated liposarcoma respond poorly to systemic therapy, therefore novel molecular targets will have to be identified to explorenew 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 ahigh-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.

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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.*

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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 [α], Mapitigama, N [σ] & Abeysena, HTCS [ρ]

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 papaniculaou (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

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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. Cyto-screeners 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

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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 5thgrade 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

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

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

Screening test +ve/-ve	Cervical HPV/DNA specimen +vefor HR-HPV	Cervical HPV/DNA specimen –vefor HR-HPV
Vaginal HPV/DNA* specimen +ve for HPV	38	06
Vaginal HPV/DNA specimen – ve for HPV	0	577
Total	**38**	**583**

**HPV/DNA- Human papillomavirus/DNA*

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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 coefficent 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 cervical specimen collection method by cobas 4800 was 1.9% (95% CI; 1.89%-1.91%) (Table 3). Percentage of HPV 16 and 18 genotypes infection positives 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

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

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

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

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 (5, 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

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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.

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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 and NM were participated in the design of the study. 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.

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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[1]. 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.*

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

Dr. Kavita Rathore [α], Dr. Manish Choudhari [σ] & Dr. Naresh Jain [ρ]

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[1]. 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.

I. Introdution

Shalakya Tantra is an important branch in Ashtang Ayurveda which deals with the diseases manifesting above supraclavicular region (Urdhwajatrugata roga)[2]. Netra Sharira deals with three major parts of eye-Mandala, Sandhi and Patala[3]. 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.Chaksyu 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.

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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, Dhumdarshi, 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[4]. 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[5]. Drishti Mandala is said to be situated just next to Krishna Mandala. As per modern ophthalmology the eyeball comprises three coats[6]:

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[7] is 1/7th of Krishna Mandala. At some places it is written 1/9th of Krishna Mandala[8]. 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[9] 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[9] (similar to cotyledons of pulses in shape), which is biconvex in shape. It supports the fact that Drishti is lens as lens is biconvex[10] in shape.

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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 Sushruta Samhita "5" Mandals[11] in the eye ball -

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

"6" Sandhi[12] in the eye ball-

Pakshma-Vartamagata Sandhi.
Vartama-Shuklagata Sandhi.
Shukla-Krishnagata Sandhi.
Krishna-Drishtigata.
Kaninaka Sandhi.
Apanga Sandhi.

"6" Patalas[13] in the eye ball-

Vartmagata Patalas-2
Akshigata Patalas-4

Name	Constituting factor
1 st Patala	Tejas + Jala (Tejojalaashrita)
2 st Patala	Mamsa (Mamsaashrita)
3 st Patala	Medas (Medoaashrita)
4 st Patala	Asthi (Asthyaashrita)

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 developed[17].
- If poison is given in Anjana form (Visha Samsrishta Anjana) then blurring of vision (Drishti vibhrama) occurs[18].
- Controlling vega (natural urges) like Kshudha and Adhovayu leads to defective vision[19,20].
- 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 Lingnasha[22]. AcharyaSushruta used term Drishti runaddhi for loss of vision in Linganasha[23].

c) Drishti in Modern View[24]

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 with a smooth shining surface.

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 illumination[25].

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.

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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).

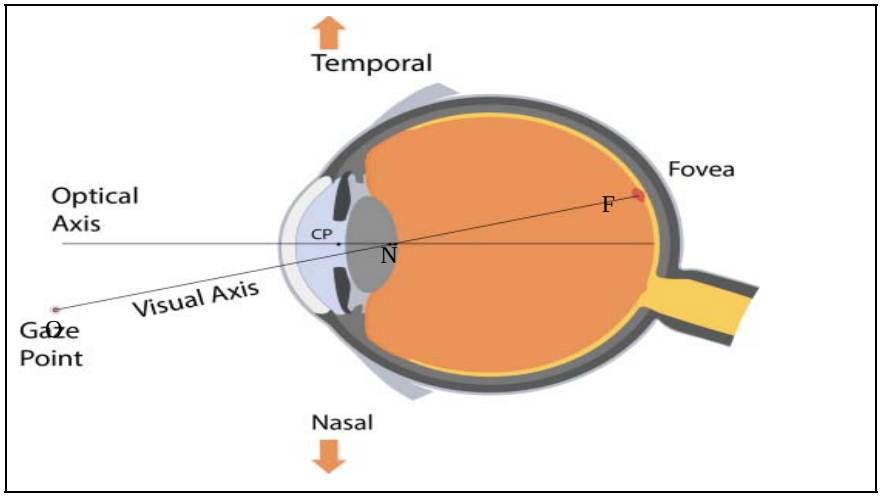


Figure 1: Visual axis (OF)

Visual pathway system: The visual pathway consists of- Optic Nerve, Optic Chiasma, Optic Tract, Lateral Geniculate Body Optic Radiations and Visual Cortex.

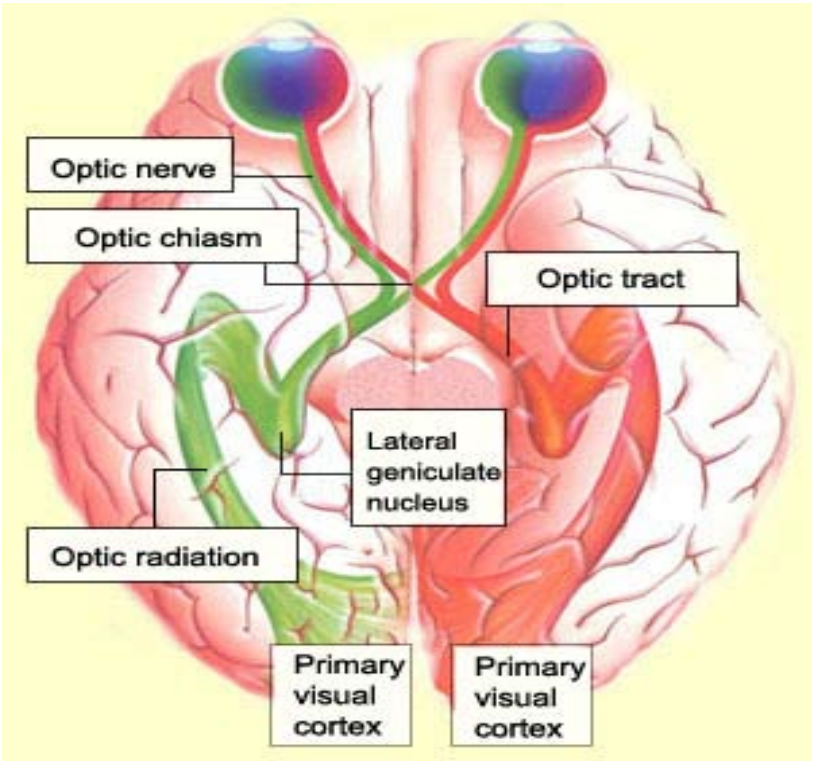


Figure 2: Visual Pathway

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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 chaksurendriya 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)

↓

Indriyaadhisthana (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 prathama 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.

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The features of patalagata doshas are listed in the table below-

S.No.	Patalas	Lakshana	Interpretation of Symptoms and signs
1	Prathama	Disturbance in vision[30]	Blurred of vision
2	Dwiteeya	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[31].	Floaters, metamorphopsia, photopsia, loss of depth perception and presbyopia
3	Triteeya	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[32].	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.
4	Chaturtha	Complete loss of vision but still the patient sees bright objects like sun, moon and Lightening[33].	Conditions where in the patient is said to be legally blind, conditionswhere there is retinal traction leading to flashes.

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 nayanaamyastu bhavantyaabhishand-nimittamula)[34]. 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 (drishtigata rogas) it should be considered as intraocular lens whereas in pitta vidagdha drishti, shleshma vidagdha drishti etc. drishtigata rogas it must be taken as optic nerve or retina as a whole.

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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 is one complication that is mostly seen in diseases such as hemolytic diseases, liver disease, and obesity. It can also be a secondary complication of long-duration use of antibiotics like ceftriaxone. However, gallbladder stone, together with sludge themselves, is unusual within the children's population. We observed three children with gallbladder stones who were on a long course of intravenous ceftriaxone. In this study, we present the three cases of children aged between eleven months to seven years who were treated with high doses and for an extended period (more than two weeks) of intravenous ceftriaxone for a complicated systemic bacterial infection. The goal of this study is to raise awareness about the possibility of developing gallbladder stones in pediatric patients who receive a long course of intravenous ceftriaxone.

Keywords: *ceftriaxone, gallbladder stone, child, complication.*

GJMR-F Classification: *NLMC Code: WI 140*



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Ceftriaxone-Induced Gallbladder Stones in Children

Dr. Maryam Al Saidi [α], Dr. Samiya Al Hashmi [σ], Dr. Nuha AlTahir [ρ] & Dr. Hilal AL Hashami [ω]

Abstract- Gallbladder stones in children is one complication that is mostly seen in diseases such as hemolytic diseases, liver disease, and obesity. It can also be a secondary complication of long-duration use of antibiotics like ceftriaxone. However, gallbladder stone, together with sludge themselves, is unusual within the children's population. We observed three children with gallbladder stones who were on a long course of intravenous ceftriaxone. In this study, we present the three cases of children aged between eleven months to seven years who were treated with high doses and for an extended period (more than two weeks) of intravenous ceftriaxone for a complicated systemic bacterial infection. The goal of this study is to raise awareness about the possibility of developing gallbladder stones in pediatric patients who receive a long course of intravenous ceftriaxone.

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I. Introduction

Gallbladder stone has been reported in both adults and children due to different complications of illness, mainly hemolytic disorder, procedure, and even with the long-term duration use of antibiotics which is being seen by ceftriaxone. It is also seen as less common in children compared to adults. Ceftriaxone is a third-generation of the cephalosporins class with a broad-spectrum antibacterial coverage and is used for the treatment of severe bacterial infections like osteomyelitis, gastrointestinal, and meningitis in the children's population [4,10]. It is far more extensively distributed in most body tissues and fluids and can penetrate blood-brain barriers into the meninges [3,4,14]. Because of the prolonged plasma half-life, it can also be excreted by the urine, and 40% is secreted by the bile duct [3], and it can be administered once daily and every 12 hours in the case of complex infection in some children.Most medications have adverse drug reactions, including ceftriaxone that has been reported as a causative agent for pseudolithiasis either in the gall bladder or renal tract [4,5,14]. It is also known as biliary pseudolithiasis or reversible Choleolithiasis 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 in an abdominal 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 intravenous ceftriaxone.

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II. Case Description

a) Case one

An eleven-month-old boy who had previously been well was brought to the Emergency Department with a diagnosis of meningoencephalitis and a history of fever, seizures, and skin rash. He later developed septic shock with a diagnosis of Disseminated intravascular coagulation (DIC) and acute kidney injury. Investigations showed high White blood cell (WBC of 23,10^9\l), high C-Reactive Protein (CRP of 153 mg\l), and initial Liver Function Test (LFT) within the normal range. Lumbar Puncture revealed: no organism in cerebrospinal fluid (CSF) in gram stain and microscopy, 4 cell/mm2 White Blood Cell, 3320 cell/mm2 Red Blood Cell, 2.73gL protein, and 2.9 mmol/l glucose.CSF culture was negative, but blood culture revealed sensitive *streptococcus pneumonia*. A radiological study with an initial head-CT scan showed ischemic change then repeated after a few days showed acute right intraparenchymal bleeding in the right parietal region measuring 15 * 15 * 8 mm surrounded by a thin rim of edema. Magnetic resonance imaging (MRI) of the head later showed a dilated ventricular system. The diagnosis of *streptococcus pneumonia* Meningitis was made based on clinical, CSF results and radiological findings. Later in his course, a ventriculoperitoneal (VP) shunt was inserted by a neurosurgery team. Ceftriaxone therapy started and was planned initially to be for four weeks. The patient developed acute abdominal pain with irritability. A pediatric radiologist performed an abdominal ultrasound, which revealed a distended gall bladder with a clump of soft calculi, indicating that ceftriaxone should be discontinued and replaced with levofloxacin. A liver function test was done by the team after ten days of ceftriaxone which revealed ALT 20 IU\L and ALP 226 IU/L.

After two weeks of stopping ceftriaxone, the abdomen ultrasound repeated and showed a single mobile echogenic focus.. After switching to intravenous levofloxacin, the child's abdominal pain improved.

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Single mobile echogenic focus; Gall bladder stone measures 8mm. Child abdominal pain improved with time, and he continued his antibiotic course with levofloxacin.

abdemen ultrasound(US)	 A.	 B.
Finding	4weeks of IV ceftriaxone :Distended GB, with echogenic foci in the dependent part, largest =10mm, likely clump of sludge or soft calculi	After Changed to Levofloxacin: Single mobile echogenic focus , GB stone measures 8mm
Treatment	26 days around 4weeks of IV ceftriaxone	After 3 weeks of Changed to Levofloxacin

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

b) Case Two

A two-year-old boy is on prophylaxis for asthma. He was presented to the pediatric Emergency Department with a history of fever for two days. It was documented to be high-grade fever 39Co, which did not respond to antipyretics. He also had a history of vomiting and productive cough associated with lethargy and reduced activity for two days. He was sluggish, irritable, dehydrated, and had a large head, more than 97th centile for his age. He also had neck stiffness. The investigations revealed leucocytosis of 28 109l, primarily neutrophils with 24 109l in the complete blood count (CBC), and a high C reactive protein of 171 mgL. Lumbar puncture revealed turbid cerebellar spinal fluid CSF with high white blood cell WBC 453UL and low glucose. Cerebrospinal fluid (CSF) culture revealed *streptococcus pneumonia*. The respiratory viral panel was positive for *parainfluenza 3*. The first radiology image was a Non-contrast CT Scan of the head which showed mild brain edema. An MRI of the head reveals right frontal-parietal meningitis with bilateral subdural effusion but no abscess. The diagnosis of complicated *streptococcus pneumonia* meningitis with bilateral subdural effusion was given to this infant. He was treated with a long course of intravenous Ceftriaxone. After week four of treatment, it noted that the child was complaining of abdominal pain. The initial ultrasound abdomen was normal, but as the child continued to complain of abdominal pain, it was repeated, and it revealed gallbladder stones, so it was decided to switch from ceftriaxone to levofloxacin for another 3-6 weeks. As noted, it was associated with a deranged liver function test (LFT) with high alkaline phosphate (ALP) of 265 IU\L, GGT=42IU/L and alanine transaminase (ALT) of 91 IU\L which is initially normal LFT. Follow up; Abdomen Ultrasound showed improvement after changing ceftriaxone to intravenous Levofloxcillion. Liver Enzyme also improved.

abdomen Ultrasound			
Finding	A. normal gallbladder GB	B. The GB is full with multiple small calculi, average=5mm, no biliary dilation	C. GB is full with multiple small calculi, same as previous, GB shows normal wall
Treatment	Ceftriaxone IV (2-3weeks almost)	Ceftriaxone IV (four months almost)	After Changed to Levofloxacin by 3weeks

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

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c) *Case Three*

A seven-year-old girl who had previously been healthy and had no previous medical illnesses. 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. She was treated for three weeks with intravenous ceftriaxone 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 bordies 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 doing well until three weeks after beginning ceftriaxone, when she presented to the ER complaining of a day of severe abdominal pain and vomiting. Her gallbladder was found to have multiple tiny calculi on abdominal ultrasound. 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 oral clindamycin. She continued on clindamycin, and her symptoms improved.

abdemen ultrasound(US)	
Finding	Distended gallbladder with multiple tiny calculi After Received IV Ceftrxione for 3 week

Figure (3): The finding of abdomen US the patient who treated with ceftriaxone for bone infection

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

Case No.	Age	sex	Ceftriaxone therapy		Biliary complication		
			Dose (mg/kg)	Duration(days)	Symptom	Onset	Types stone /sludge
1	11months	M	100 mg/kg/days	21 days	Abdomen pain	After 3 weeks from started ceftriaxone	Distended GB likely clump of sludge or soft calculi
2	2years	M	100 mg/kg/days	120 days	Abdomen pain & irritable	After 4months from started ceftriaxone	multiple small calculi, no biliary dilation
3	7years	F	100 mg/kg/days	26 days	Abdomen pain vomiting	After 4 weeks from started ceftriaxone	Distended gallbladder with multiple tiny calculi

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III. Discussion and Literature Review

There are limited studies that have looked into ceftriaxone-induced gallstones in the children's population. Within most literature reviews, gallbladder stone occurs because of organic cause or illness, but few numbers reported predisposing factors with the specific type of antibiotics use that presented as symptomatic illness. Ceftriaxone is a broad-spectrum antimicrobial agent. It is one of the third-generation cephalosporin. It has a broad-spectrum effect against most bacterial infections, 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 this as a result of genetic/genome variation on the UGT1A1 gene, which encodes the enzyme UDP-glucuronosyltransferase (UDP).This enzyme acts on glucuronidation and formation of bile salts that transform small lipophilic molecules, (i.e., steroids, bilirubin, and drugs) into water-soluble (Fretzayas et al., 2011) [14,15].

In our study, we reported three cases of children with an age ranging from eleven months to seven years treated in tertiary hospital for severe bacterial infection. One of the children, a seven-year-old female, was referred from an orthopedic clinic to pediatric infectious diseases services for further evaluation and management of her acute osteomyelitis of the left distal femur and proximal tibia.children,The remaining two cases were 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= 91/IU/L and high GGT=42IU/L). The other two children had a normal range of laboratory findings with blood count and liver enzymes). Abdomen Ultrasound, for two children, showed a distended gallbladder with multiple tiny calculi/clumps or soft calculi, which was done at three weeks of intravenous ceftriaxone. The abdomen US of the third child showed that the GB is filled with multiple small calculi, average=5mm, nobiliary dilation. The pediatric surgery team was also involved, but none of the patients required any surgical intervention.

After the abdomen US findings, ceftriaxone was discontinued for all cases. In the two patients with meningitis, ceftriaxone changed to Levofloxacin, and therefore the other case of osteomyelitis was changed to clindamycin. All children didn't require other medications. All investigations normalized after discontinuing ceftriaxone. Abdomen ultrasound repeated and showed improvement in gall stones together with normalized 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 discovered that all three patients had the same incidental finding of pseudolithiasis in the abdomen Ultrasound [4.15].The same findings were reported in an Iranian study; different predisposing factors cause Choleolithiasis 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 the majority of cases in the children group as represented with a high 27.3% during a study compared to hematological disorder.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 a high dose of ceftriaxone along with a prolonged 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, Choleolithiasis 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.

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IV. Conclusion

Prolonged use (more than two weeks) of intravenous Ceftriaxone, a third-generation cephalosporin with broad antibacterial activity against a variety of bacterial infections, is a known risk factor for gallbladder stone in both adults and children.

The correct diagnosis of ceftriaxone-induced gallstone was usually delayed as most of the patients are asymptomatic and most cases were detected only by incidental radiological findings. These findings promote 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: ursodeoxycholic 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.

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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*

SURVIVALANALYSISFORPANCREATICCANCERPATIENTSUSINGCOXPROPORTIONALHAZARDCPHMODEL

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Survival Analysis for Pancreatic Cancer Patients using Cox-Proportional Hazard (CPH) Model

Aditya Chakraborty [α] & Chris P. Tsokos [σ]

Abstract- Pancreatic cancer is comparatively rare but extremely lethal. In the United States, pancreatic cancer is the 4*th* leading cause of cancer death, and in Europe, it is the 6*th*. 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. 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.

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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.

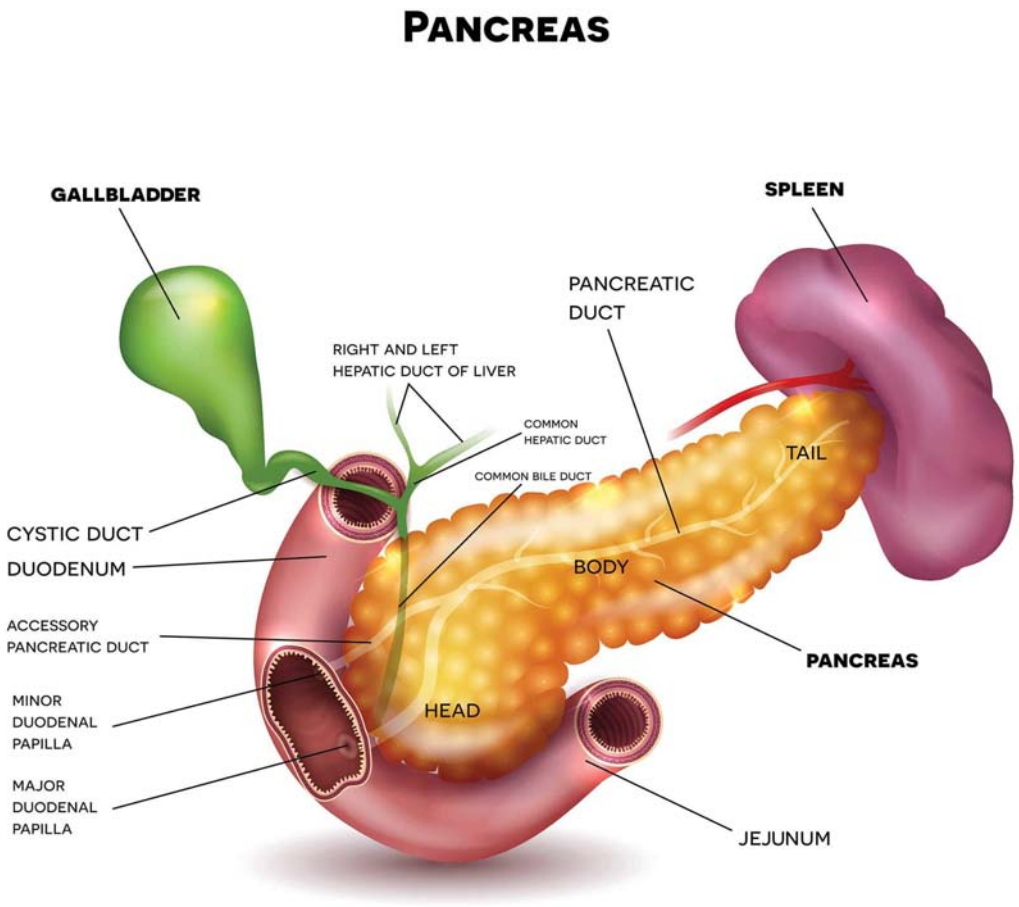


Figure 1: Different Parts of the Pancreas

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

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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?

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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.

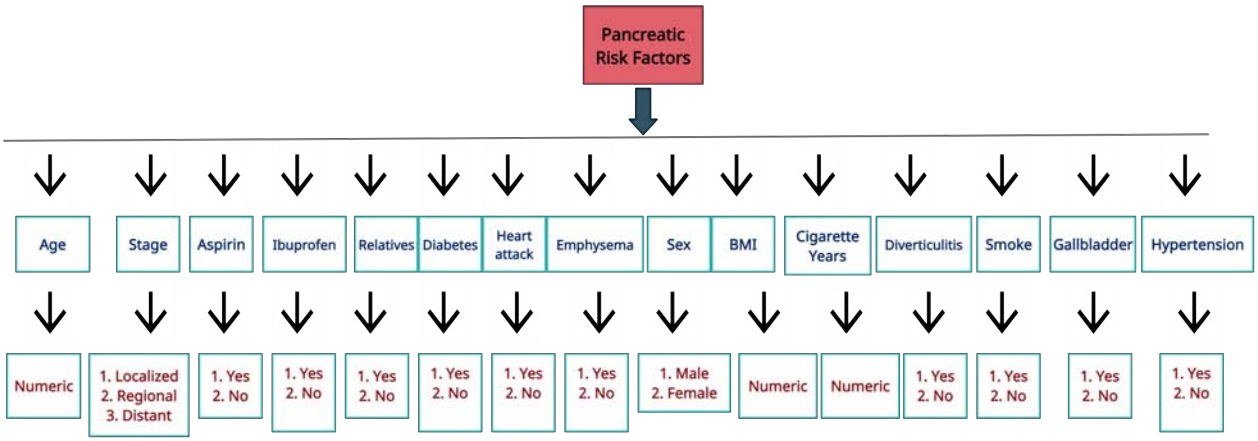


Figure 2: Pancreatic Cancer Data with Relevant Risk Factors

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

$$F_T(t) = P(T \leq t) = \int_0^t f(t)dt \ ,$$

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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:

$$S(t) = P(T \geq t) = 1 - F_T(t) = \int_t^{\infty} f(t)dt \ . \tag{1}$$

$S(t)$ 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,

$$f(t) = \frac{dF_T(t)}{dt} = -\frac{dS(t)}{dt} \ . \tag{2}$$

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:

$$\begin{aligned} h(t) &= \lim_{\Delta t \to 0} \frac{P\{t \leq T < t + \Delta t \mid T \geq t\}}{\Delta t} \\ &= \lim_{\Delta t \to 0} \frac{P\{t \leq T < t + \Delta t\}}{\Delta t} \frac{1}{S(t)} \\ &= \frac{f(t)}{S(t)} \ . \end{aligned} \tag{3}$$

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

$$h(t) = -\frac{d}{dt} log\{S(t)\} \ . \tag{4}$$

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,

$$S(t) = exp\Big[-\int_0^t h(u)du \Big] \ . \tag{5}$$

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

$$f(t) = h(t)exp\Big[-\int_0^t h(u)du \Big] \ . \tag{6}$$

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

$$H(t) = \int_0^t h(u)du = -lnS(t) \ . \tag{7}$$

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:

$$h_i(t) = \lambda_0(t)exp\Big[\sum_{j=1}^{p} \beta_j X_{ij} + \sum_{j \neq k} \eta_{jk} X_{ij} X_{ik} \Big] \ , \ \ j, k = 1, 2, \ldots, p. \tag{8}$$

In the above expression, λ_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. β_j measures the impact of X_{ij} on $h_i(t)$. η_{jk} is the interaction coefficient between j^{th} and k^{th} risk factor of the i^{th} individual and

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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,

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

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 *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).

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 ($AIC = 2ln(L) + 2k$, 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 *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),

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

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.

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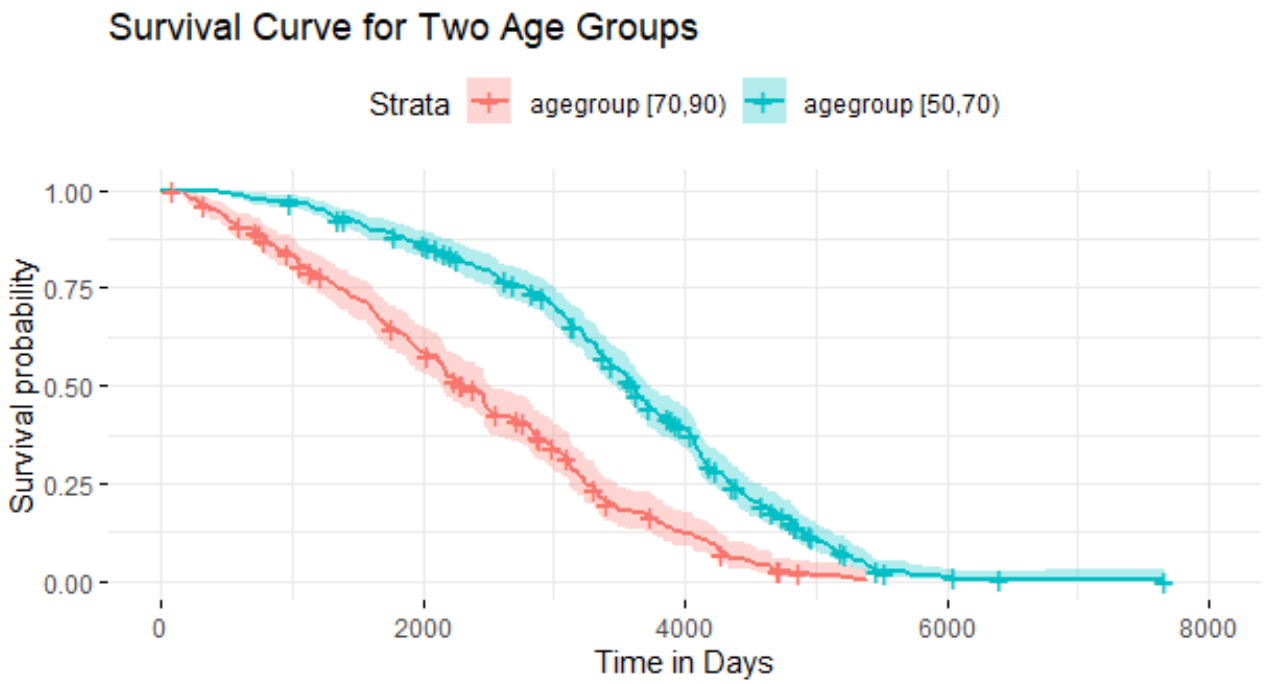


Figure 3: The Estimated Survival Curve for the two different Age Groups

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.

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

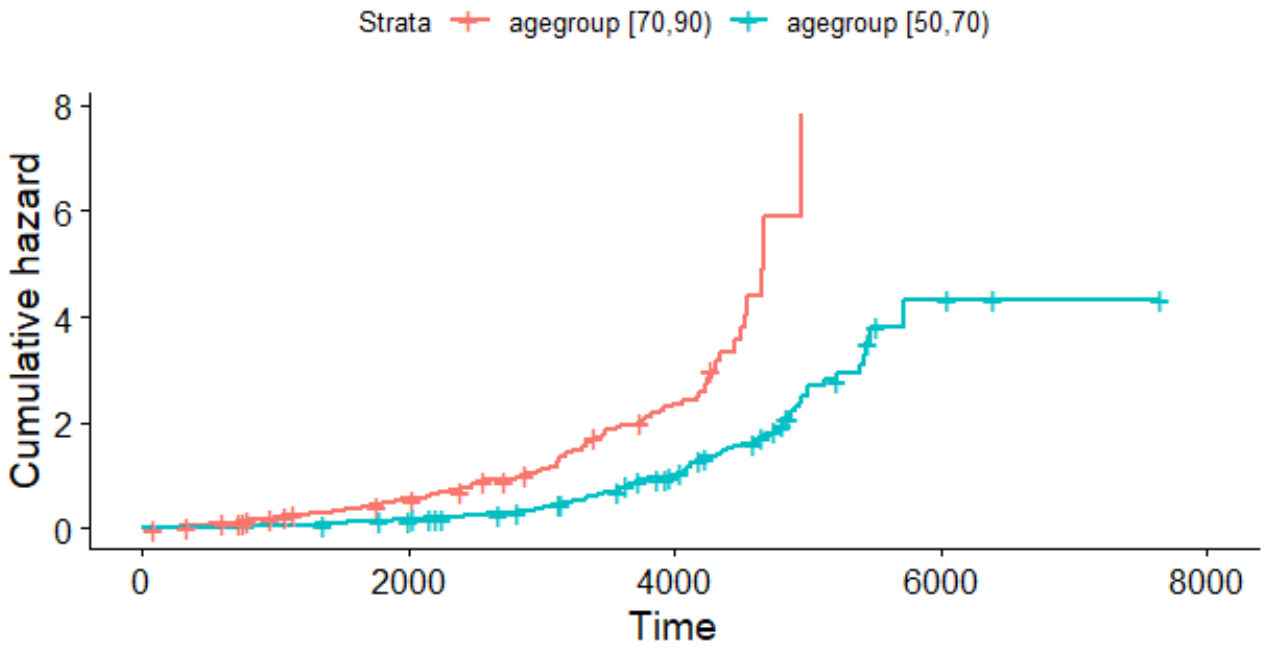


Figure 4: Cumulative Hazard Functions of the Two Age Groups

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

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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

Risk Factors		**Count**
Stage	Localized	135
	Regional	178
	Distant	364
Aspirin	Yes	333
	No	344
Ibuprofen	Yes	168
	No	509
Relatives	Yes	650
	No	27
Diabetes	Yes	83
	No	594
Heart attack	Yes	84
	No	593
Emphysema	Yes	19
	No	658
Sex	Male	388
	Female	289
BMI		677
Cigarette Years		677
Diverticulosis	Yes	41
	No	636
Smoke	Yes	404
	No	273
Gallbladder	Yes	98
	No	579
Hypertension	Yes	256
	No	421

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:

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$$\widehat{ln\Big[\frac{h_i(t)}{\lambda_0(t)}\Big]} = \begin{cases} 0.3X_{2R} + .5X_{2D} - .53X_{3Y} \\ +.61X_{4Y} - .37X_{15Y} + .87X_{6Y} \\ -.6X_{5Y} - .7X_{8Y} \\ -.35X_{9F} + .0037X_{11} - .51X_{12Y} + .15X_{13Y} \\ +.28X_{14Y} - .56X_{4Y}X_{13Y} + .41X_{3Y}X_{9F} \\ +.6X_{3Y}X_{15Y} + .01X_{2R}X_{11} + .68X_{12Y}X_{9F} \\ +.32X_{15Y}X_{9F} - .47X_{15Y}X_{14Y} \\ -.52X_{2R}X_{4Y} + 2.18X_{2R}X_{8Y} + .8X_{15Y}X_{12Y} \end{cases} \tag{11}$$

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:

$$h_i(t; X_{ij}, X_{ij}X_{ik}) = h_{0s}(t)exp\Big[\sum_{j=1}^{p}\hat{\beta}_j X_{ij} + \sum_{j\neq k}\hat{\eta}_{jk}X_{ij}X_{ik}\Big],\ j \neq k \tag{12}$$

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;

$$\begin{aligned} \hat{S}_i(t; X_{ij}, X_{ij}X_{ik}) &= exp\Big[-\int_0^t h_i(t; X_{ij}, X_{ij}X_{ik})dt\Big] \\ &= exp\Big[-\int_0^t h_{0s}(t)exp\Big[\sum_{j=1}^{p}\hat{\beta}_j X_{ij} + \sum_{j\neq k}\hat{\eta_{jk}}X_{ij}X_{ik}\Big]dt\Big] \\ &= exp\Big[exp\Big[\sum_{j=1}^{p}\hat{\beta}_j X_{ij} + \sum_{j\neq k}\hat{\eta_{jk}}X_{ij}X_{ik}\Big]\Big(-\int_0^t h_{0s}(t)dt\Big)\Big] \\ &= exp\Big(-\int_0^t h_{0s}(t)dt\Big)^{\Big[\sum_{j=1}^{p}\hat{\beta}_j X_{ij} + \sum_{j\neq k}\hat{\eta_{jk}}X_{ij}X_{ik}\Big]} \\ &= \big[S_{0s}(t)\big]^{\Big[\sum_{j=1}^{p}\hat{\beta}_j X_{ij} + \sum_{j\neq k}\hat{\eta_{jk}}X_{ij}X_{ik}\Big]} \end{aligned} \tag{13}$$

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

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ratio (HR). Thus, we rank from the most contributing risk factor to the least contributing risk factor to pancreatic cancer patient's death or survival times.

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

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

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 ($\hat{\beta} > 0$) implies higher hazard rate, and thus a bad prognostic factor. on the contrary , a negative estimated coefficient/weight ($\hat{\beta} < 0$) 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.

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Table 3: Global Statistical Significance of the Model

Test	Test Statistics Value	df	p-value
Likelihood Ratio Test	96.6	34	$7*10^{-8}$
Wald Test	100.8	34	$2*10^{-8}$
Score (log-rank) Test	109.9	34	$6*10^{-10}$

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 (18) (19) 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 $\mathscr{R}_i$ be the risk set at time T_i denoted as $\mathscr{R}_i = \{j : T_j \geq T_i\}$. Given the setup, the *partial likelihood*, proposed by Cox (1975) is defined by:

$$L(\beta) = \sum_{i=1}^{n} \delta_i \Big[\beta^T Z_i - log\Big[\sum_{j \in \mathscr{R}_i} exp(\beta^T Z_j)\Big]\Big] \quad . \tag{14}$$

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

$$\hat{r}_i = Z_{(i)} - \frac{\sum_{j \in \mathscr{R}_i} Z_j exp(\hat{\beta}^T Z_j)}{\sum_{j \in \mathscr{R}_i} exp(\hat{\beta}^T Z_j)} \quad . \tag{15}$$

   The following Figures 5 and 6 illustrate the plot of the scaled Shoenfeld 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).

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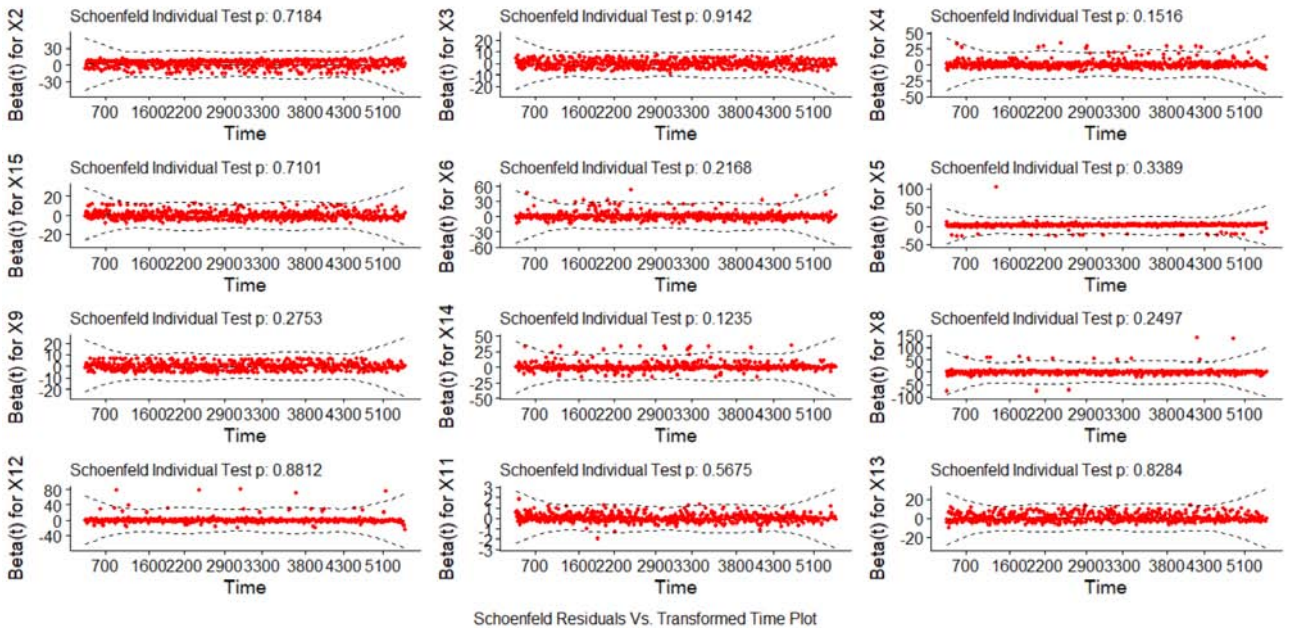


Figure 5: Testing Proportional Hazard Assumption for Individual Risk Factors

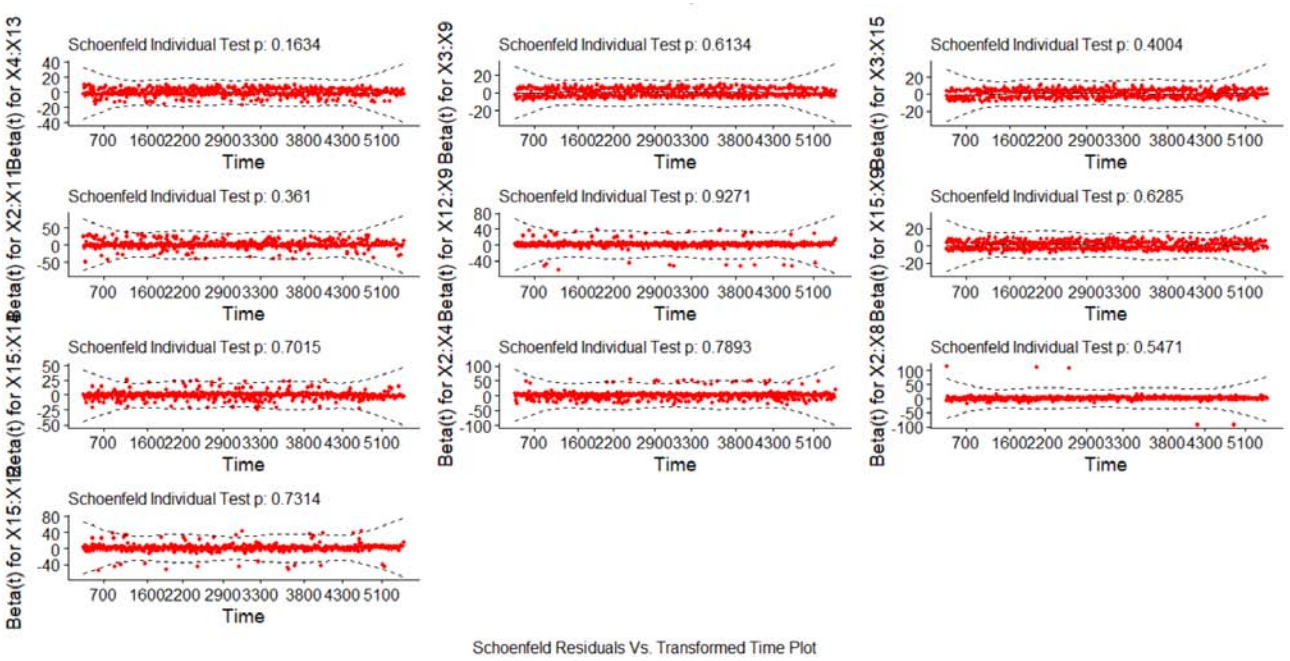


Figure 6: Testing Proportional Hazard Assumption for all Interactions

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.

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Table 4: Testing Proportional Hazard Assumption

Risk Factors	χ^2	p-value
X_2	.66	.72
X_3	.01	.91
X_4	2.05	.15
X_{15}	.14	.71
X_7	3.39	.1
X_6	1.5	.21
X_8	1.3	.25
X_{12}	.02	.88
X_{14}	2.37	.12
X_{13}	.05	.82
X_{11}	.32	.56
X_{10}	2.56	.11
X_5	2.16	.34
X_9	1.19	.27
$X_4 \bigcap X_{13}$	1.94	.16
$X_3 \bigcap X_9$	.25	.61
$X_3 \bigcap X_{15}$	.71	.4
$X_2 \bigcap X_{11}$	.04	.36
$X_{12} \bigcap X_9$	.008	.93
$X_{15} \bigcap X_9$	.23	.63
$X_{15} \bigcap X_{14}$	.14	.7
$X_2 \bigcap X_4$	.47	.79
$X_2 \bigcap X_8$	1.2	.55
$X_{15} \bigcap X_{12}$	.12	.73
GLOBAL	44.17	.1

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 *martingle residual*, proposed by Therneau and Grambsch (21) is given by,

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

where δ_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, M_i, have a skewed distribution. We have, $\hat{M}_i = 1$ for for maximum possible values and $\hat{M}_i = -\infty$

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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 $\hat{M}_i$ correspond to patients who were alive for a long time.

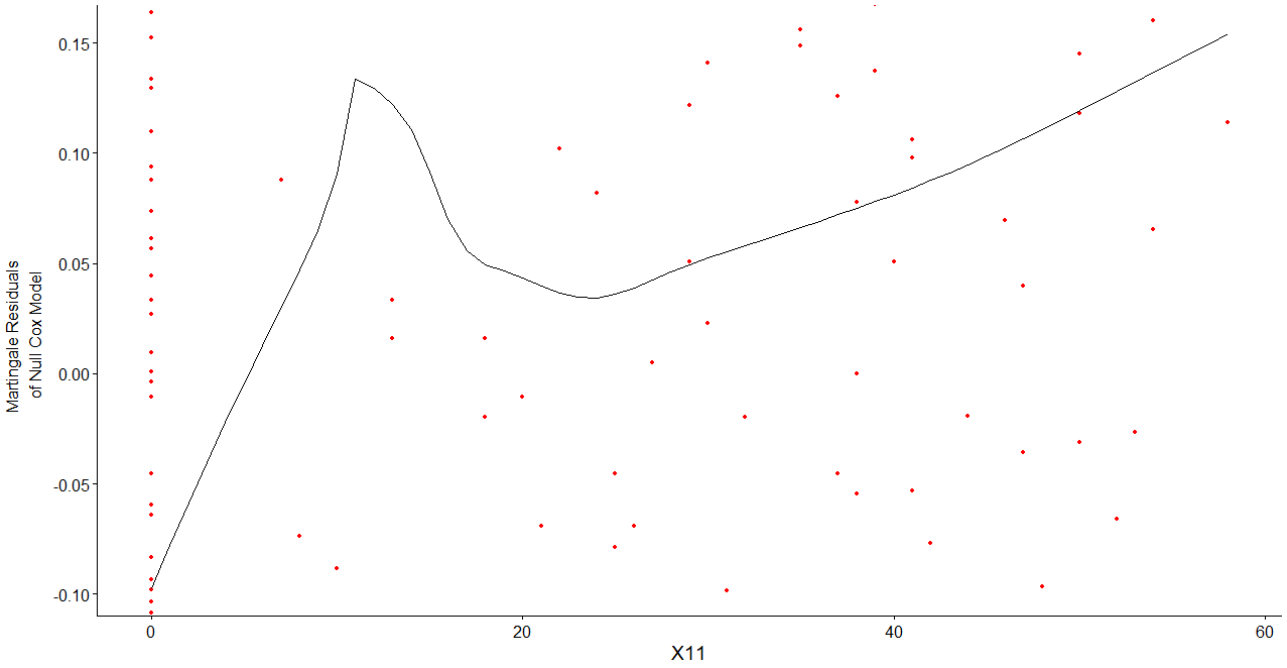


Figure 7: Validating the Linearity Assumption of the Continuous Covariate

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 β_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.

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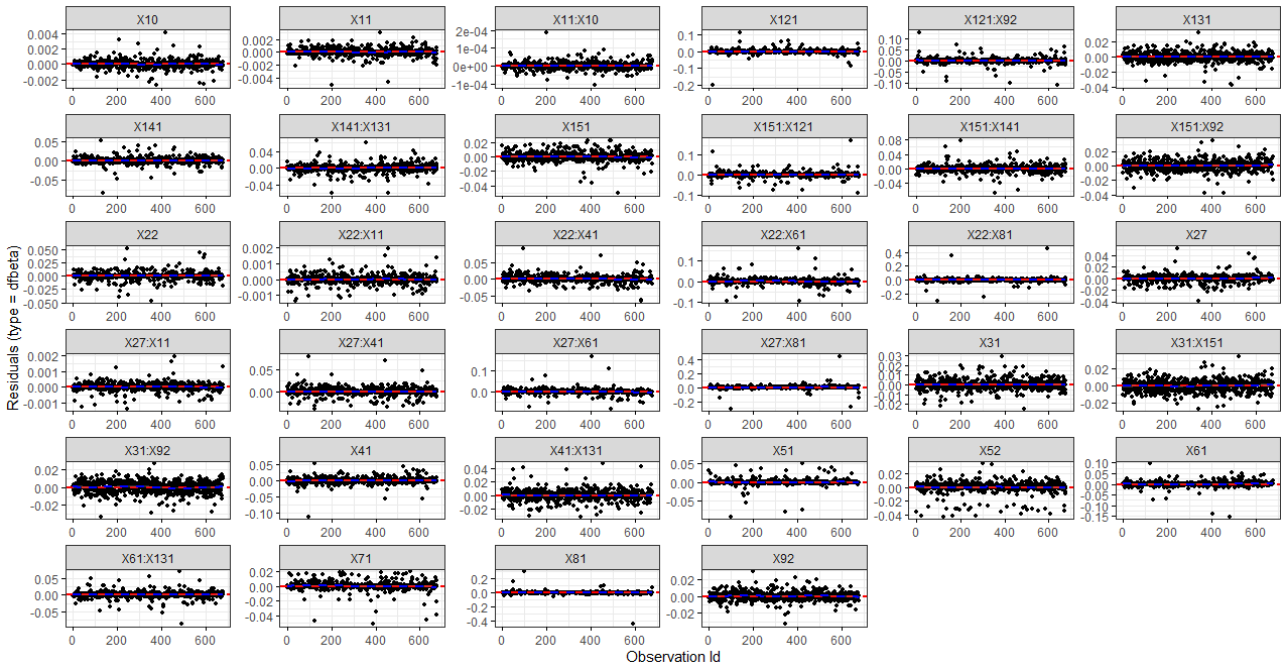


Figure 8: Assessing Influential Observations in the Model by dfbeta

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.

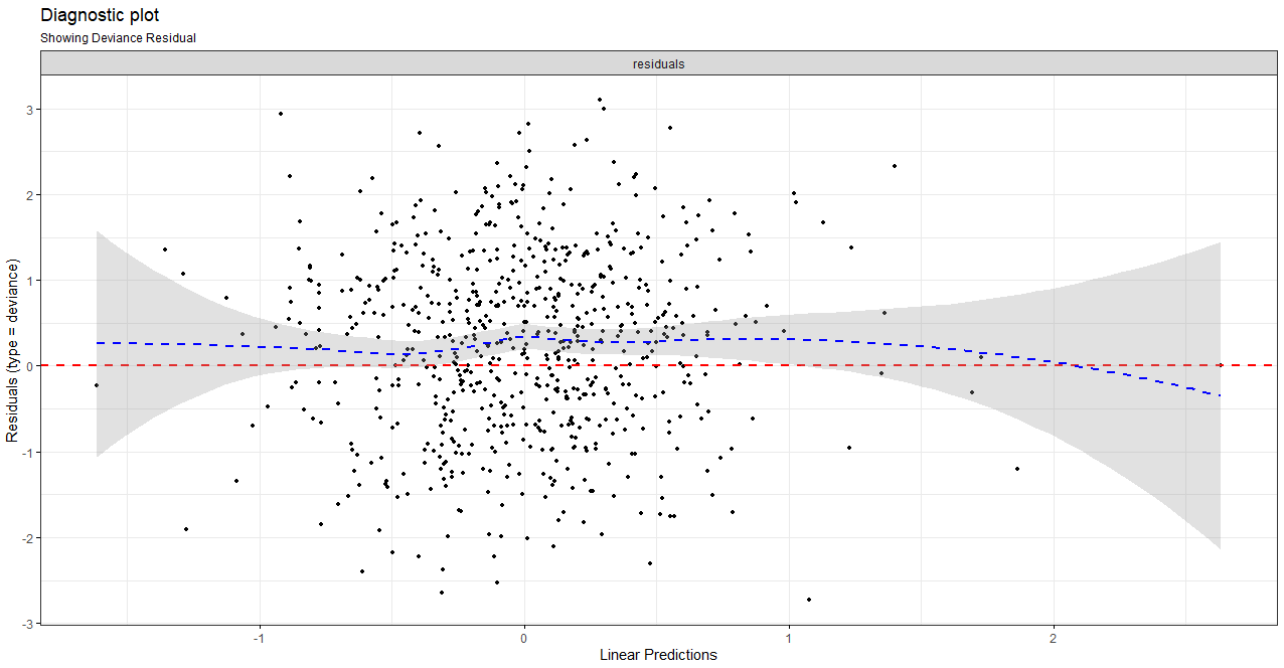


Figure 9: Assessing Influential Observations in the Model by Deviance Residual

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

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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

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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.

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There are no competing interests to declare.

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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 though 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.



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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.



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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

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

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