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Mucosal-Invariant T Cell Receptor Recognizes HLA-DRB1 Selected SARS-Epitopes

By Subhajit Dasgupta, Shaoni Dasgupta & Mausumi Bandyopadhyay

Abstract- Infection of SARS-COV2 and its variants causes wide range morbidity and mortality in recent years. Identification of epitope-based mechanism of viral infection with progressive fatality and antiviral immunotherapy are two major goals to address population-bias immune response. We selected peptides from SARS-COV2 Spike (6VXX_A), Delta (B.1.617.2), Omicron (B.1.1.529) proteins. These peptides contain epitopes which are identified as low rank good fit immunogenic as recognized more by HLA-DRB1*15:01, than HLA-DRB1*07:01 and HLA-DRB1*03:01. We also found the selected epitopes specifically form interactive complex with mucosa-associated invariant T cell. The Molecular Docking and Molecular Dynamics experiments demonstrated amino acid sequence-specific interaction between close atoms from epitopes and MAIT-TCR. We used virus unrelated microbial peptide antigen85 as control.

Keywords: *SARCOV2; Spike peptides; Epitope; HLA-DR; T cell, T cell receptor, mucosa.*

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Mucosal-Invariant T Cell Receptor Recognizes HLA-DRB1 Selected SARS-Epitopes

HLA-DRB1, MAIT-TCR Selection of SARS Epitopes

Subhajit Dasgupta [α], Shaoni Dasgupta [σ] & Mausumi Bandyopadhyay [ρ]

Abstract- Infection of SARS-COV2 and its variants causes wide range morbidity and mortality in recent years. Identification of epitope-based mechanism of viral infection with progressive fatality and antiviral immunotherapy are two major goals to address population-bias immune response. We selected peptides from SARS-COV2 Spike (6VXX_A), Delta (B.1.617.2), Omicron (B.1.1.529) proteins. These peptides contain epitopes which are identified as low rank good fit immunogenic as recognized more by HLA-DRB1*15:01, than HLA-DRB1*07:01 and HLA-DRB1*03:01. We also found the selected epitopes specifically form interactive complex with mucosa-associated invariant T cell. The Molecular Docking and Molecular Dynamics experiments demonstrated amino acid sequence-specific interaction between close atoms from epitopes and MAIT-TCR. We used virus unrelated microbial peptide antigen85 as control. The root -mean square deviation (RMSD) values ranges between 2.5-6.2 Angstrom unit with cut off value 2 Angstrom demonstrate good to moderate alignment between TCR and epitopes. The level of significance ($p<0.05$) of epitope binding with MAIT-TCR was determined as compared with control. Overall, the results introduced a new set of viral spike epitopes which generate specific mucosal immune response involving invariant T cells.

Keywords: SARCOV2; Spike peptides; Epitope; HLA-DR; T cell, T cell receptor, mucosa.

I. Introduction

Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-COV2) infection caused pandemic (COVID-19) in recent years 2019-2021 with high mortality rate (1-4). The pre-existing pulmonary conditions worsen the clinical outcome during infection. Recent emergence of Delta and Omicron variants with advent of subvariants clearly indicate a range of fast transforming viruses appear in diverse human population (5-7). The genetic predisposition for intrinsic susceptibility of human populations towards SARS-COV2 and variants Delta, Omicron is still unclear. Also, the specific role of T helper cells, its receptors and T cell repertoires in viral antigen recognition for antiviral immune response is not known yet. Several reports suggested involvement of HLA responses in SARS-COV2 infection and after vaccination (8-10). Though we still have unresolved questions to address: (1) HLA allele specificity for antigen presentation and population bias expression patterns; (2) T helper cell expansion and TCR specificity towards viral antigens. The reports from different laboratories suggest HLA-DR deficiency or low expression in monocytes is associated with immunosuppression and severity in SARS-COV2 infected patients (11-14). In particular, specificity of HLA-DRB1 alleles to recognize Delta and Omicron variants of SARS-COV2 and T cell receptor specificity towards epitopes is unclear yet but critical for evaluating hosts' protective immune response.

We identified immunogenic epitopes from N-terminal first nine hundred- amino acid sequence of SARS-COV2 (COVID 19), Delta variant (B.1.617.2) and Omicron Variant (B.1.1.529) Spike proteins. We found HLA-DRB1 allele specificity for these selected Spike epitopes is determinant for recognition by mucosa-associated invariant T cell receptor in human population.

II. Materials and Methods

a) *SARS-COV2 and its variant protein sequences*

The N-terminal first 900 amino acid Spike protein sequence is selected from NCBI protein databases (SARS-COV2: 6VXX_A, Delta variant (B. 1.617.2): 7ORB_R, Omicron (B.1.1.529): 7Q09_A. The protein sequence was processed by NCBI protein blast (pblast) software engine to determine 60 amino acid peptide strings. The randomly selected 25-30 Spike peptide strings containing epitopes were processed for protein database (PDB) file by using Avogadro (USA). The Omicron Spike epitope PDB files: OM42, OM60, M312, M370 and SARS-COV2 (6VXX_A)-Delta variant (7ORB_R) overlapping CD4 immunogenic epitope -PDB file DLT1, Delta variant (7ORB_R) epitope DLT2 (Table 1) are used to determine close alignment and binding efficiency with mucosa associated invariant T cell receptor Vα7.2Vβ7.2 (MAIT-TCR).

b) *Epitope sequence identification from Spike protein of SAR-COV2, Delta, Omicron Variants*

The CD4- recognizing epitope sequences were identified from N terminal nine hundred amino acid sequences of virus Spike envelope protein. The amino acid sequences were analyzed for their immunogenicity by Immune Epitope Database (IEDB) software engine

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(NIAID, USA). The IEDB Tools were programmed to analyze 7 allele response to virus Spike proteins following methods described by Dhanda et al. (15). The HLA-DRB1*03:01, HLA-DRB1*07:01 and HLA-DRB1* 15:01 responsive epitopes were selected for determining specific binding affinity with MAIT- TCR.

c) Molecular Docking and Molecular dynamics

The selected peptide epitopes from N terminal first nine hundred amino acid sequence are processed by Avogadro software (USA) for construction of protein database (PDB). These PDB sequences are allowed to run (100 nanosecond) for close alignment with mucosa associated invariant T cell receptor (PDB: 4L9L). The specifications include recognition of alpha helical structure for interaction, speed 30 frames per second with Ray trace. The epitopes are placed as mobile and the TCR is placed as target. The molecular dynamics experiments ran for 10 cycles with cut off value 2 Angstrom unit. After completion of the run, the frame per nanosecond was calculated under Executive Root Mean Square Deviation (RMSD) value ranging from 5.2-6.2 Angstrom unit (RMSD: 2 Angstrom indicates good homology between interacting protein sequences thus closer to bind together). The aligned interacting peptide epitope with TCR protein sequence is recorded by Molecular Dynamics method by using Schrodinger PyMol software (USA). The Molecular Docking of Spike epitopes on TCR is determined in the same experiment at different time points.

d) Statistics

ANOVA is used to determine significance ($p < 0.05$ at least) level of interaction profiles (Frame/ nanosec) between selected virus epitope and with respect to unrelated virus peptides. Mycobacterium avium antigen85 peptide was used as control to determine significant binding of virus epitopes with MAIT-TCR selective amino acid sequence.

III. Results

T cell specificity of SARS-COV2 Spike peptides is critical for prolong antiviral responses leading towards development of memory. However, it is unclear whether localized TCR - immune response in mucosal layers have specificity towards SARS-COV2 -Spike epitopes? It is also unclear whether Cytotoxic T cells (CD8), natural killer T cells (NKT) and other localized invariant T cells have specific response towards HLA-DRB1 allele specific immunogenic Spike epitopes.

In order address the questions, we first screened the viral epitopes derived from N (NH2)-terminal first 900 amino acid sequence of SARS-COV2 and its variant Delta, Omicron (Described in Methods section). Then, we selected each of these epitopes and analyzed their immunogenicity with respect to binding with HLA-DRB1*03:01, HLA-DRB1*07:01 and HLA-DRB1*15:01. These HLA-DRB1 allele recognized viral epitopes are checked for their efficacy for CD4 and TCR recognition. Here, we presented recognition ability of mucosa-associated invariant T cell receptor (MAIT-TCR) to the selected epitopes derived from Spike envelop protein sequences of SARS-COV2 , Delta and Omicron variants.

a) Recognition of N-terminal Spike epitopes of SARS-COV2 and Delta variant by HLA-DRB1 alleles

The results presented in the Figure 1 show differential responses of screened N-terminal Spike epitopes of SARS-COV2 (ID 6VXX_A) (Fig.1A) and Delta variant (7ORB_R) (Fig.1B) towards HLA-DRB1 alleles 03:01, 07:01 and 15:01. The bar diagrams with epitope database analysis tool (IEDB) percentile ranks demonstrate a base line of 20 percentile; below which the epitopes are low immunogenic and good fit to HLA-DRB1 alleles. These epitopes have ability to induce moderate to low CD4 responses. The results showed overlapping recognition of epitope LYNSASFST (derived from 6VXX_A and 7ORB_R) by HLA-DRB1*03:01and HLA- DRB1*15:01 (< 20 percentile rank) for SARS-COV2 and Delta variant. HLA-DRB1*07:01 recognition of the same epitope showed marginally over than 20 percentile rank. The epitope has lower rank (45.38232) when it is recognized by HLA-DRB1*15:01 and HLA-DRB1*03:01. The epitope YFKIYSKHT (rank: 42.8908) derived from SARS-COV2 Spike protein (ID 6VXX_A) is recognized by HLA-DRB1*15:01 and HLA-DRB1*07:01 while another epitope peptide VSLLSVLLM/ LVSLLSVLL (rank: 50.16648/ 52.20664) is recognized by all three tested HLA- DRB1*03:01, HLA-DRB1*07:01 and HLA-DRB1*15:01alleles. The specific recognition by HLA-DRB1*07:01 and HLA-DRB1*15:01 allele is detected for Delta variant epitope FASVYAWNR (rank: 43.9931), YAWNRKRIS (rank: 40.04248), YRLFRKSNL (34.09812). These HLA-DRB1 selected Spike epitopes from SARS-COV2 and Delta variants are immunogenic to CD4 T cells in human populations.

b) Recognition of N-terminal Spike epitopes of Omicron variant by HLADRB1 alleles

The recently detected Omicron variant (B.1.1.529) in post pandemic period human population raise another question on protective antiviral responses of existing vaccines and drugs. The presence of several mutations in the virus RNA genome with possible quick adaptation ability in human population bring the variants as highly infectious and transmissible subtypes of SARS- COV2. To determine epitope recognition patterns by HLA-DRB1 alleles, the N-terminal amino acid sequences of Omicron variant (B.1.1.529) Spike protein was selected from protein database, Sequence ID 7QO7_A (NCBI) and screened for CD4 immunogenicity by using IEDB Tools software as mentioned in the Methods section above. The first one thousand amino acid containing sequence was processed for

constructing protein database (PDB) files. The Omicron PDB files OM42 (amino acid 1-42); OM60 (amino acid 43-60); M312 (amino acid 312-342), M370 (amino acid 343-370) are constructed similarly as mentioned above. The Table 2 demonstrates overlapping 15-amino acid Omicron peptide sequences (highlighted part of the sequences). The first three epitope peptides in the Table 2 show the lowest rank (5.11, 9.77 and 21) indicating good fit recognition by HLA-DRB1*15:01 as compared with HLA-DRB1*03:01 and HLA-DRB1*07:01. The peptide epitopes in the Table 2 demonstrate moderate to higher HLA-DRB1 recognition patterns not only for 15:01 but 03:01 and 07:01 alleles, thus range poor to non-immunogenic to CD4.

c) *Mucosa associated invariant T cell receptor (MAIT-TCR) binding with Spike epitopes*

The specificity of virus epitope induced activation of human immune system is determined by demonstration of sequence specific recognition of virus epitopes with T cell receptor. In the aspect, we wanted to determine the interaction and close binding profiles of TCR and our selected CD4 immunogenic virus epitopes. We found; selected epitopes are recognized by CD4 to a variable extent generating over all low to moderate CD4 response (with respect to HLA-DR recognition pattern). The mucosal associated invariant T cells (MAIT) are conserved lineage of CD4-CD8-/CD4-CD8+ T cell subset in human population (16-19). MAIT cells express Valpha7.2/Jalpha33 alpha chain paired with Vbeta2 beta chain. The MAIT-TCR Valpha domain has similarity with type 1 invariant natural killer T (iNKT) cells like CD1 positive cells which respond to different microbial pathogens and autoimmune manifestations (20).

We wanted to determine efficacy of the selected immunogenic SARS-COV2 and variant Spike epitopes (Table1) to form close binding interaction with MAIT-TCR (PDB: 4L9L).

The protein database (PDB) files of virus epitopes (Table 1) are allowed to interact with mucosal associated invariant T cell receptor (MAIT-TCR) by molecular docking and molecular dynamics experiments. Figure 2A shows efficient binding between DLT2 and TCR 4L9L at the amino acid sequence 1 to 9 region (Square box showing specific alignment between epitope sequence DLT2 and TCR 4L9L). The RMSD value: 2.309 (Fig. 2B) indicates close alignment with more sequence homology thereby efficient binding between DLT2 epitope and MAIT- TCR.

The figure 2C demonstrates alignment between interacting Delta epitope DLT1 and MAIT-TCR at amino acid sequence 1 to 9 region. The efficiency of binding between DLT1 epitope and TCR 4L9L is determined by root mean square deviation (RMSD) value: 5.410 Angstrom (Fig. 2D). The RMSD value indicates moderate to less sequence homology between interacting peptides thereby moderate to low binding as compared with RMSD value for DLT2 and TCR interaction.

The results presented in figure 3 A demonstrate an aligned binding between Omicron Spike epitope (PDB: OM42) and MAIT- TCR (PDB: 4L9L) sequences. The arrowhead and a square box show the region of binding of OM42 with TCR protein sequence. The digital experimentation using Schrodinger PyMol software identified 1-6 amino acid sequence in TCR binds with OM42 Omicron epitope (the square box indicates aligned amino acid sequences). The 100-nanosecond run with 30 frames/ nanosecond output for 10 cycles demonstrates atom to atom interaction profile between target TCR and mobile OM42 (Fig.3B). The executive root mean square deviation (RMSD) value 6.612 Angstrom shows relative differences between interacting atoms from epitope OM42 and TCR 4L9L. The epitope OM60 binds with MAIT- TCR at 1-26 amino acid region (square box shows the sequence interactions) (Fig.3C). Corresponding molecular dynamics show higher root mean square value (RMSD: 7.282) (Fig.3D). The observation indicates less alignment between interacting atoms of OM60 and TCR 4L9L.

Omicron epitope M312 (amino acid sequence 1-31) is shown to bind with TCR 4L9L (amino acid sequence 11-41) (Fig. 3E). The corresponding molecular dynamics experiments demonstrate root mean square deviation (RMSD) value 6.131 Angstrom which indicate less sequence homology, more deviation between interacting atoms leading toward moderate binding between Omicron epitope M312 and MAIT TCR (Fig.3F). The epitope M370 demonstrates binding of M370 amino acid sequence 1 to 26 with MAIT-TCR 4L9L amino acid sequence 1 to 26 (the box shows interacting sequences) (Fig. 3G). The molecular dynamics experiments show 100 nanoseconds run with 30 frames per nanosecond in which atomic interactions between Omicron epitope M370 and MAIT-TCR exhibit recognizable differences with moderate alignment between two different sequences close enough to bind each other. The root- mean square value RMSD: 6.364 Angstrom indicate difference between the atomic interactions with rendering time (Fig. 3H).

The specificity of viral epitope binding with MAIT-TCR (4L9L) is determined by deletion peptide sequences in which sequential three amino acid deletion was performed to construct new set of peptides. These deletion peptide constructs were processed for PDB files and allowed to interact with MAIT -TCR. The root- mean square deviation (RMSD) (5 to ≤ 2 Angstrom) values demonstrate specific binding of virus epitope with TCR (data not shown).

In order to find out specificity of binding between virus Spike envelop protein epitopes and MAIT-TCR in the molecular dynamics experiments, we use single factor ANOVA to determine significant differences

between number of frame per nanosecond values derived from Omicron Spike epitopes OM42, OM60, M312, M370 and SAR-COV2, Delta variant epitopes DLT1, DLT2 from control peptide: antigen85 (*Mycobacterium avium* soluble antigen, unrelated to virus protein). The results demonstrate significance level at $p < 0.05$ between control number of frame per nanosecond and that of all Omicron epitopes interacting with MAIT-TCR in molecular dynamics experiments. The frame per second value of SAR-COV2 and Delta epitope also demonstrate significant differences ($p<0.05$) with respect to control molecular dynamics with MAIT-TCR.

The observations suggest such a marked difference in receptor-ligand interaction patterns between SAR-COV2, Delta and Omicron peptide epitopes with MAIT-TCR as compared with unrelated control peptide antigen85 is due to difference in mean oscillation pattern between interacting atoms of receptor and ligands close to each other. The lower the RMSD value the closer the interacting atoms are so probability of bond formation increases.

IV. Discussion

SARS-COV2 and its variants Delta and recent emergent Omicron viruses cause severe to mild respiratory tract infection in worldwide human population. The available reports from 2019 till ongoing 2022, we found severity of infection and mortality during pandemic to post pandemic period depends largely on uncontrolled heightened immune response leading inflammation and tissue damage (21, 22). However, recognition patterns of SARS-COV2 Spike protein epitopes to T cell repertoire and long-term memory immune response is still unclear. We consider the (a) antigenicity of Spike epitopes on its recognition to HLA-DRB1 alleles and (b) optimum T cell receptor response to HLA-DRB1 allele(s)-recognized epitopes are two requirements to activate T helper cells for clonal expansion and development of memory cell pool. So far, we do not see distinct memory cell pool and expansion of T helper cell repertoire during secondary infection in human population. The experimental vaccines show 6 months' time period of moderate protection. Here the question is whether the Spike peptide epitopes have ability to activate T cytotoxic (CD8) cells and Natural Killer cells more than T helper cells ? We tested T helper cell (CD4) immunogenicity and generalized T cell receptor (TCR) responses to first thousand N - terminal Spike epitopes screened through recognition patterns of HLA-DRB1*03:1, HLA- DRB1*07:1 and HLA-DRB1*15:1 (Dasgupta, unpublished observations) through computer guided molecular docking process. We extended our findings to address the question: What is the specificity of localized mucosal layer immune responses to the SARS-COV2 and its variants' Spike epitopes in human population? We seek explanation which will lead us to find out specific entry mechanisms of SARS-COV2 and its variants via first layer mucosal epithelial cells of respiratory tract, gastrointestinal tract and urogenital tract of human beings. Susceptibility is also a question as, within a population, not everyone acquired infection with same degree of severity to moribund or mortality. In this aspect, the degree of HLA-DRB1 alleles recognition to virus epitopes and MAIT-TCR response in a population have immense role towards localized inflammation leading severity.

Our findings showed specific interactions with binding affinity of mucosal associated invariant T cell-receptors (MAIT-TCR) for HLA-DRB1 allele -screened N-terminal Spike epitopes. The amino acid sequence specificity of the epitopes with MAIT- TCR is determined by molecular docking and molecular dynamics experiments.

Mucosal-associated invariant T cells are separate pool of lymphocytes belong to cytotoxic (CD8) and natural killer T cell (NKT) population in human which are known to recognize human Major histocompatibility Complex Class I related protein 1 (MR 1) and CD1d (23), (24), (16). The innate like T cells reside within tissues and share characteristics with alpha-beta and gamma- delta T cells. The antiviral effect of MAIT cells has been found in hepatitis B virus related hepatocellular carcinoma (25). Recent investigations demonstrated active role of MAIT cells in anti-tumor cell therapy approach for hematological malignancy (26), inflammation in central nervous system (CNS) during multiple sclerosis (MS) (27). Wang et al. (28) demonstrated presence of TRAV1-$^{2+}$CD8^{+} MAIT cells and NCAM1^{hi}CD160^{+} NK cells in asymptomatic COVID-19 patients. These findings relate presence of innate-like MAIT cells during inflammatory responses in different tissues. The epitope specificity of SARS-COV2 and variants are found for innate immune responder TLR8 during versatile immune responses including brain (29). The observations presented here demonstrated critical role of HLA-DRB1*03:1, 07:1 and 15:1 recognition pattern for N-terminal Spike epitopes of SARS-COV2 and its variants Delta and Omicron for optimum immunogenicity which further led to sequence specific response by MAIT-TCR. Overall, experiments demonstrate recognition of the selected viral epitopes by population-predominant HLA-DRB1 alleles is a prime immunological phenomenon which in turn activates localized invariant T (MAIT) cells via MAIT-TCR to induce antiviral defense during infection.

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Table 1: Epitope peptide sequence- protein database files

Protein Database (PDB) files	Epitope inserted peptide sequences
OM42 Omicron Spike (B.1.1.529)	SSQCVNLTTRTQLPPAYTNSFTRGVYYPDK(SEQ. 12- 30)
OM60 Omicron Spike (B.1.1.529)	VFRSSVLHSTQDLFLPFFSNVTWFHVISGT(SEQ. 31-60)
M312 Omicron Spike (B.1.1.529)	TSNFRVQPTESIVRFPNITNLCPFDEVFNAT(SEQ. 312-342)
M370 Omicron Spike (B.1.1.529)	RFASVYAWNRKRISNCVADYSVLYNLAPF(SEQ. 343- 371)
DLT1 Delta Spike (B.1.617.2)	FASVYAWNR (SEQ.24- 32)
DLT2 SARS-COV2 and Delta Spike (B.1.617.2)	LYNSASFST Delta Spike (7ORB_R: SEQ.45-53) SARS-COV2 (6VXX_A: SEQ: 397-405)

#Epitope sequences are selected from SARS-COV2 Omicron variant Spike envelop protein sequence (B.1.1529), seq id 7QO9_A, SARS-COV2 Spike protein 6VXX_A and Delta variant (7 ORB_R) (B.1.617.2).

Table 2: HLA-DRB1 recognition of epitope peptides from first thousand N- terminal amino acid sequences of SARS-COV2 Omicron variant B. 1.1.529 (7QO9_A).

Epitope Peptides	Length	HLA-DRB1* 03:01	07:01	15:01
MF**VFLVLLPLVSSQCVN**	1-17	74.94	52.80	5.11
MFV**FLVLLPLVSSQCVNL**	1-18	76.95	73.99	9.77
FVFLVLLPLVSSQCVNL	2-18	40.88	37.47	5.11
VLLPLVSSQCVNLTTRTQ	6-23	79.91	106.55	59.19
LLPLVSSQCVNLTTR	7-21	17	28	21
LLP**LVSSQCVNLTTRTQL**	7-24	65.11	79.91	62.15
LPL**VSSQCVNLTTRTQLP**	8-25	65.11	121.35	68.07
P**LVSSQCVNLTTRTQL**	9-24	20.78	39.25	61.18

SARS-COV2 Omicron variant peptides (selected from the first thousand N terminal amino acid sequence) are analyzed by Immune database Tools (IEDB Tools) for their HLA-DRB1 allele recognition and CD4 immunogenic recognition ability. The lowest score indicates the most effective towards immunogenic response.

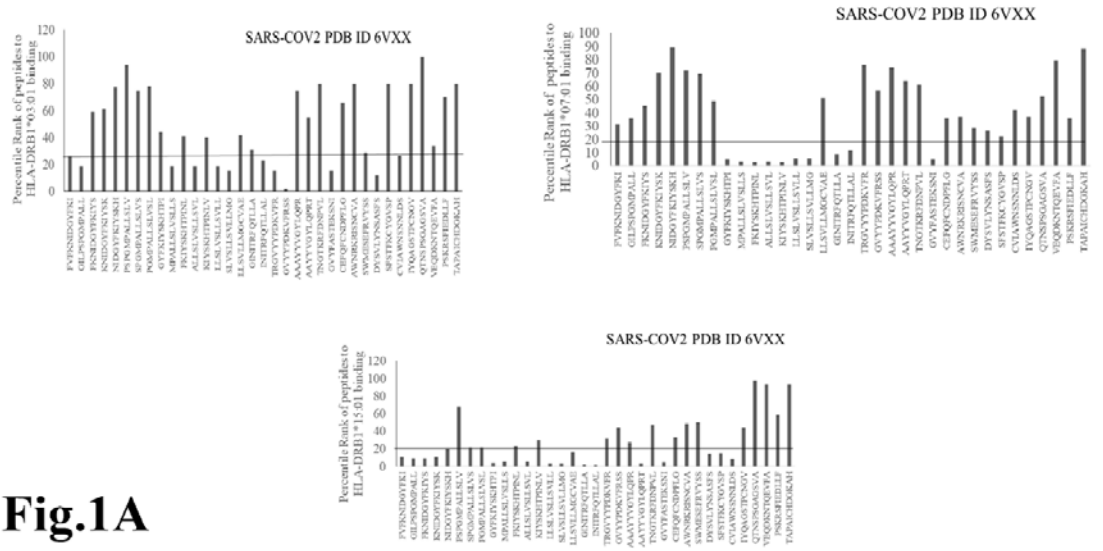


Fig.1A

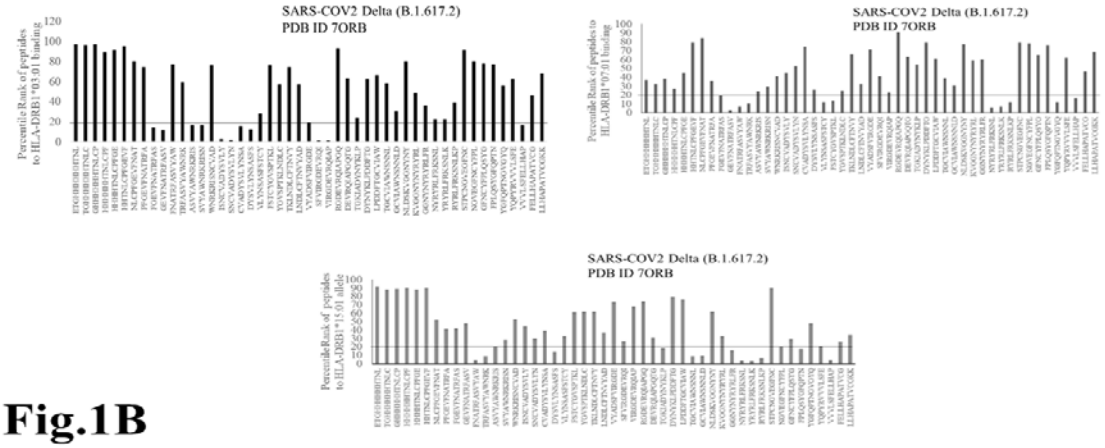


Fig.1B

Fig.1 A, B: Selection of immunogenic T cell specific epitopes by HLA-DRB1 alleles from Spike envelop protein of (A) SARS-COV2 (6VXX_A) and (B) Delta variant (B.1.617.2) virus. The Spike envelop proteins are selected from protein database. The 60 amino acid peptide strings are processed by Immune Epitope Database (IEDB) Tool software system. The tool was programmed for detecting 12 amino acid epitope peptides responding to HLA-DRB1*03:01, HLA- DRB1*07:01 and HLA-DRB1*15:01 alleles representing population based immunogenic responses. (A) Immunogenic Spike epitopes from SARS-COV2 6VXX_A protein are mapped on the basis of percentile rank determining binding affinity to HLA-DRB1. The base line of 20 percentile range is shown in the plot. The epitopes below this line are low immunogenic and good fit to corresponding HLA-DRB1 alleles. (B) Immunogenic Spike epitopes from Delta variant (B.1.617.2) are mapped in a similar way and scaled through 20 percentile base line. The low rank immunogenic peptide epitopes are found below 20 percentile rank line. Each bar in the plot represents percentile HLA-DRB1 alleles 03:01, 07:01, 15:01 responses to each of the peptide epitopes presented in the figure.

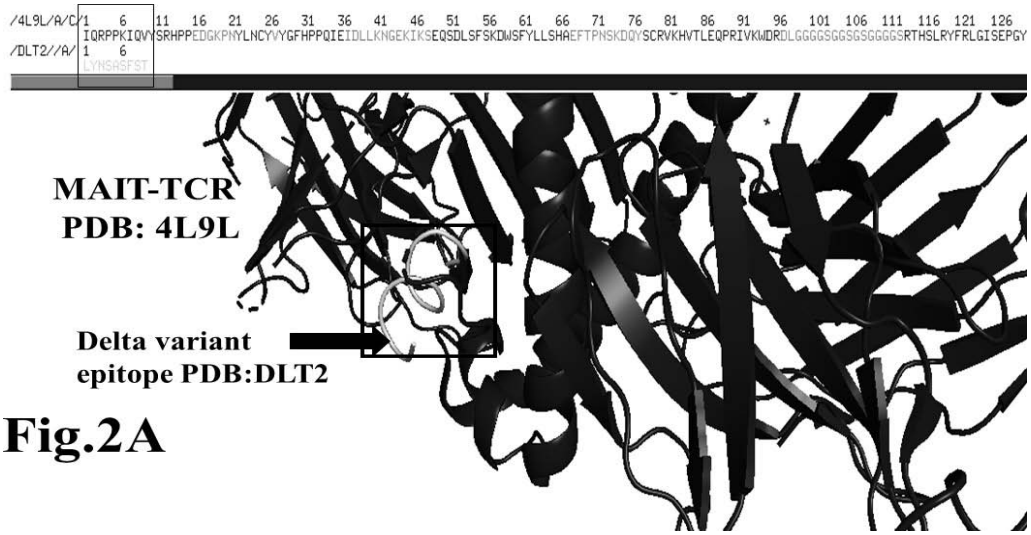


Fig.2A

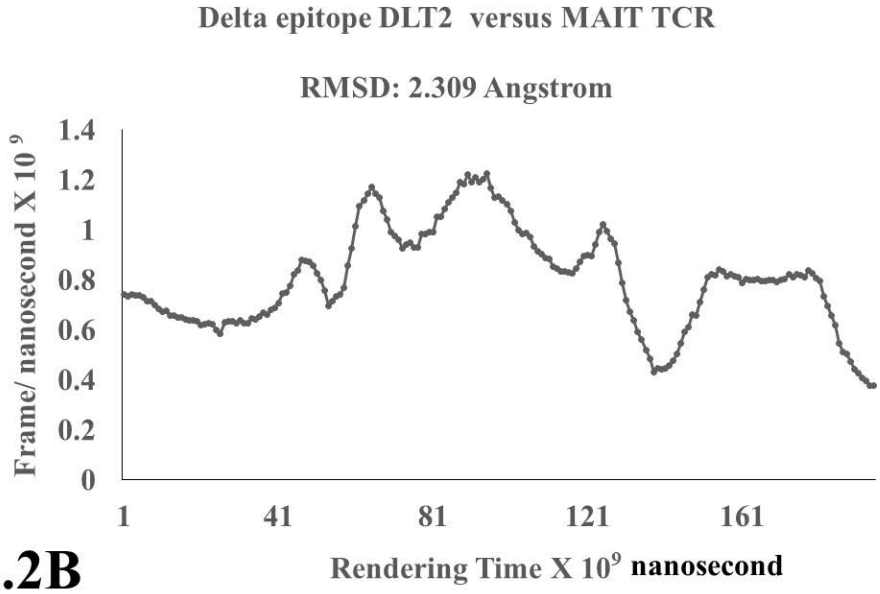
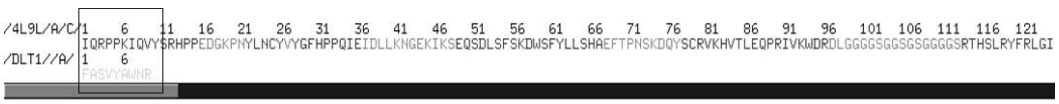


Fig.2B



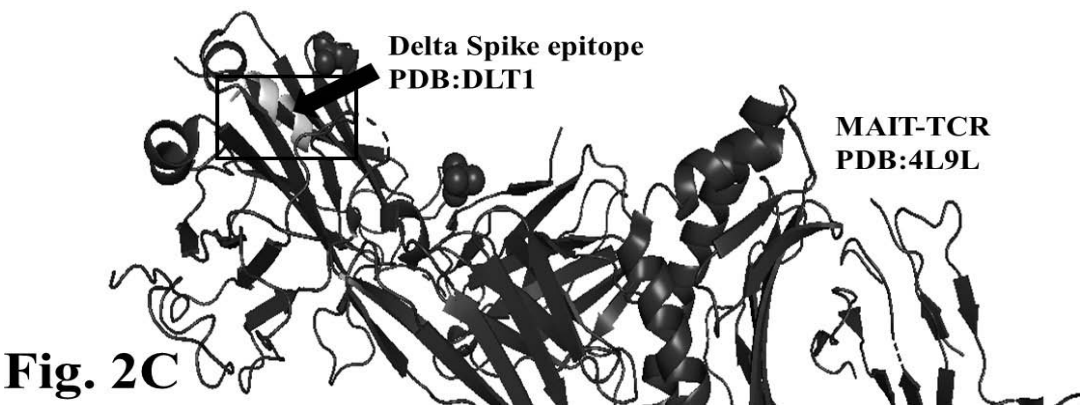


Fig. 2C

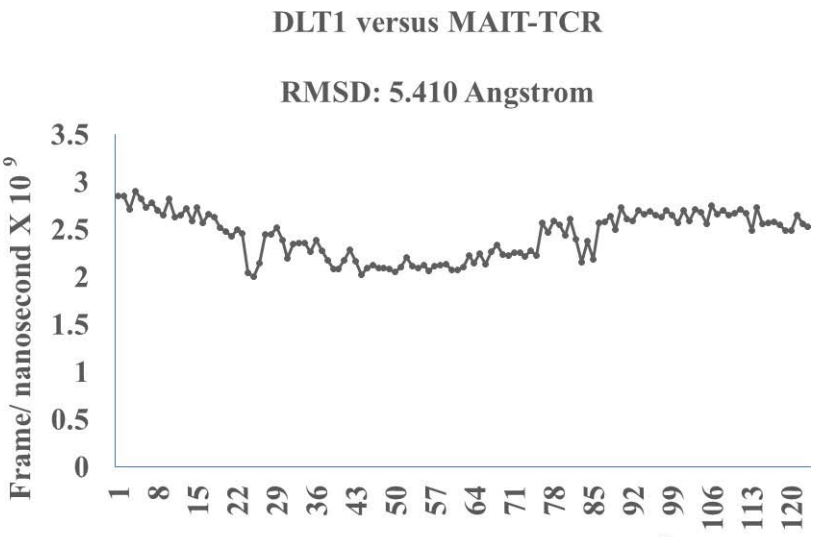


Fig. 2D

Fig.2 A, B, C, D: Determination of specific binding of immunogenic Spike epitope sequences from SARS-COV2 and Delta variant (B.1.617.2) with mucosa-associated invariant T cell receptor (MAIT-TCR). The specific binding patterns between the closest aligned atoms within cut off distance 2 Angstrom are determined by 10 cycle Molecular Dynamics alignment assay using epitopes as mobile unit and MAIT-TCR is the target for none to one interaction. The root mean square deviation (RMSD, Angstrom) for each experiment between epitope peptide and MAIT- TCR demonstrate good fit alignment. The lesser RMSD, the better is the alignment thus represents better binding. The protein database files (PDB) are used in the experiments. (A) The molecular docking of Delta variant epitope DLT2 (shown by arrow) binds with MAIT-TCR. The amino acid sequence specific alignment is shown in a box at the top of the figure. The binding area is also shown by a box in the figure. (B) The molecular dynamics experiment demonstrates binding pattern of interacting atoms between DLT2 (PDB) and MAIT-TCR (PDB: 4L9L). RMSD: 2.309 Angstrom. (C) The molecular docking of Delta Spike epitope (DLT1) with MAIT-TCR (PDB: 4L9L). The interacting protein sequences are shown in a box at the top of the figure. The binding of DLT1 by MAIT-TCR is shown in a box in the figure. (D) The molecular dynamics experiment demonstrates binding pattern of interacting atoms between DLT1 (PDB) and MAIT-TCR (PDB: 4L9L). RMSD: 5.410 Angstrom. All these interaction events in the Molecular Dynamics experiments are based on oscillation at the rate of 30 frame per nanosecond for 100 nanosecond duration as described in Materials and Methods. Statistical significance ($p<0.05$) of the frame per nanosecond values of experimental epitope peptides as compared with unrelated control peptide antigen85 with respect to MAIT-TCR has been determined by one factor ANOVA.

Anova: Single Factor

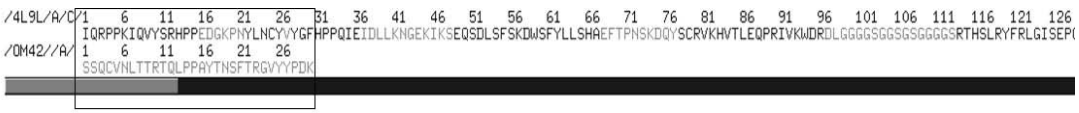
SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
Control	42	35.47787	0.844711	0.00052
DLT1	42	104.2915	2.483131	0.061207
DLT2	42	27.92395	0.664856	0.001887

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	84.32049	2	42.16024	1988.244	2.22E-94	3.069894
Within Groups	2.608186	123	0.021205			
Total	86.92867	125				

Fig 2 (A- D) Statistical significance ($p< 0.05$) for binding and close atomic interactions was determined by one factor ANOVA between Frame per nanosecond (Angstrom) value of identified SARSCOV2 Delta N terminal spike epitopes Spike epitopes and Control unrelated *Mycobacterium avium* antigen 85 peptide. Results obtained from Molecular Dynamics experiments (Fig 2A to D).



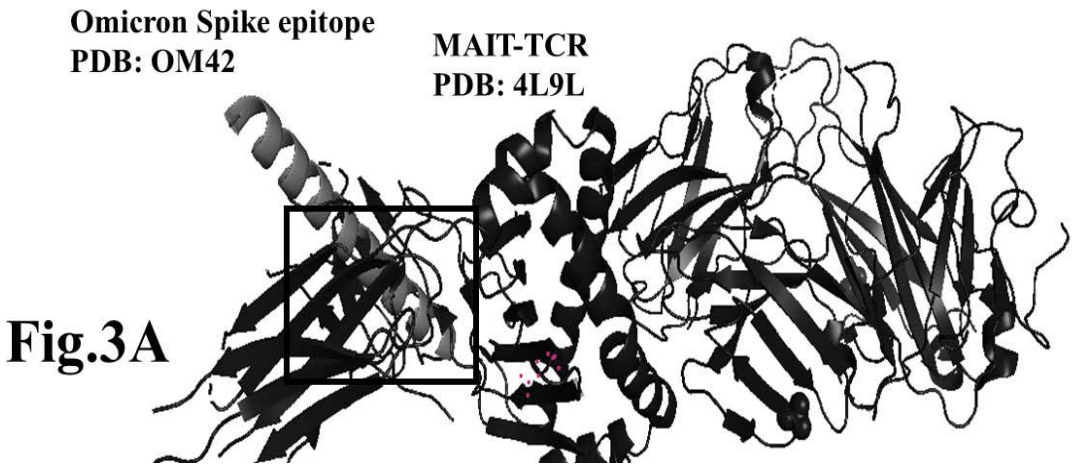


Fig.3A

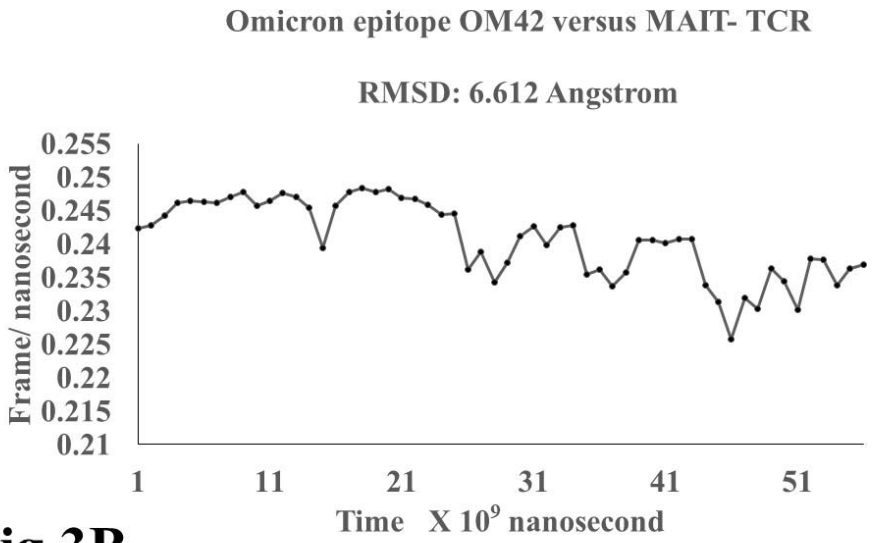


Fig.3B

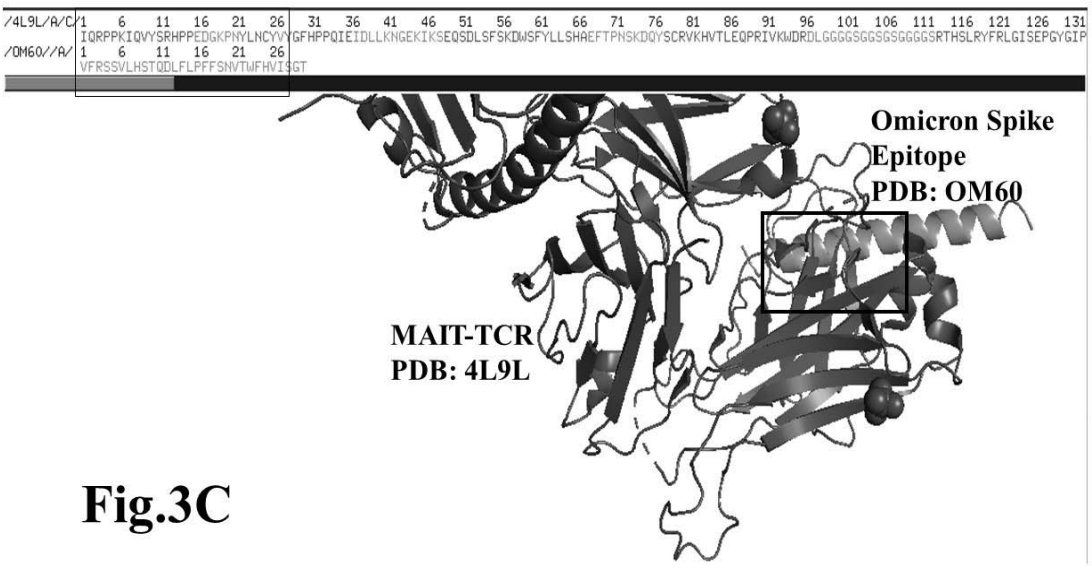


Fig.3C

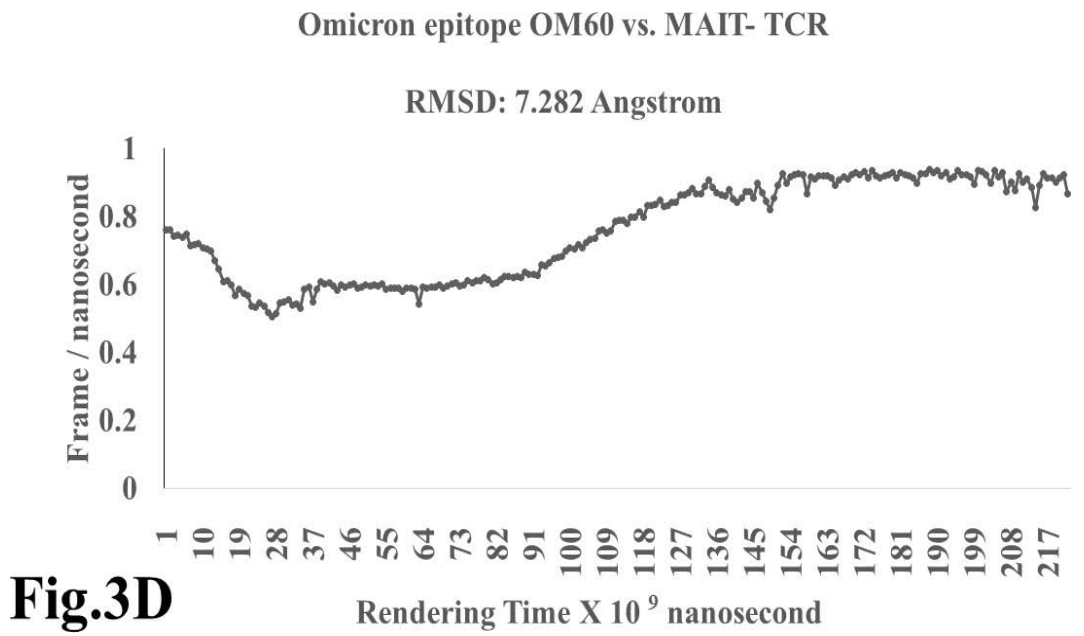


Fig.3D

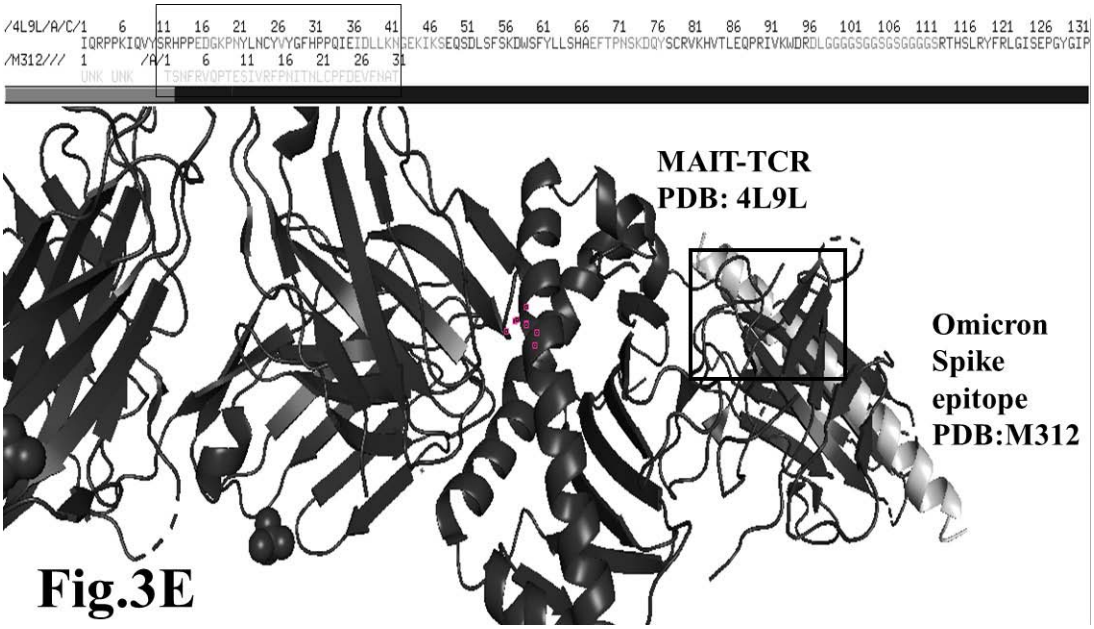


Fig.3E

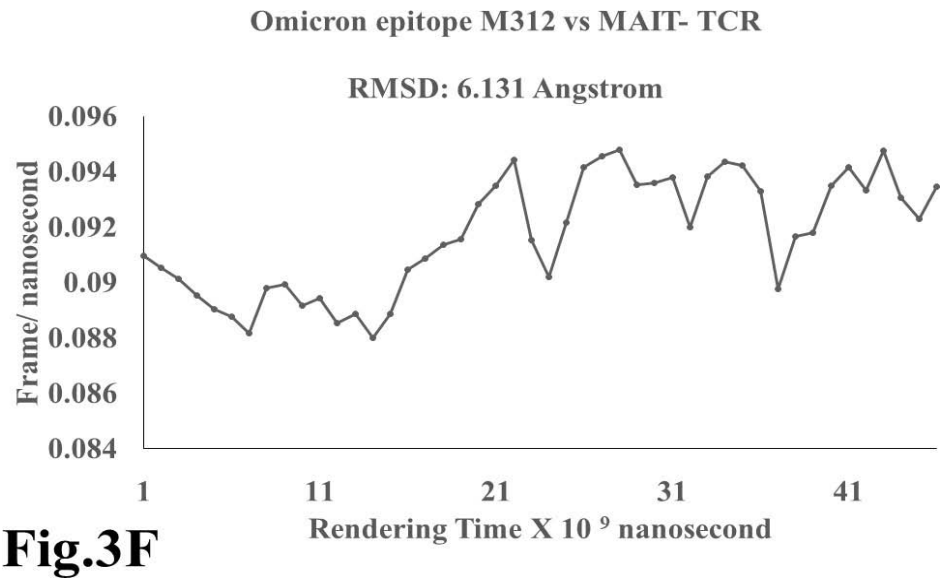


Fig.3F

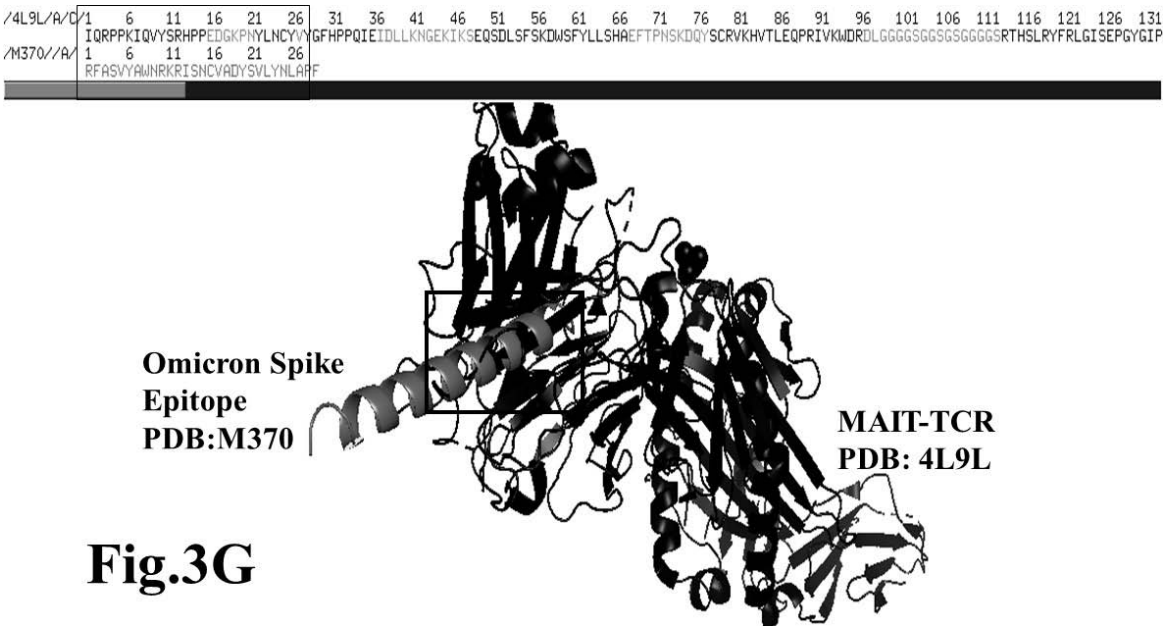


Fig.3G

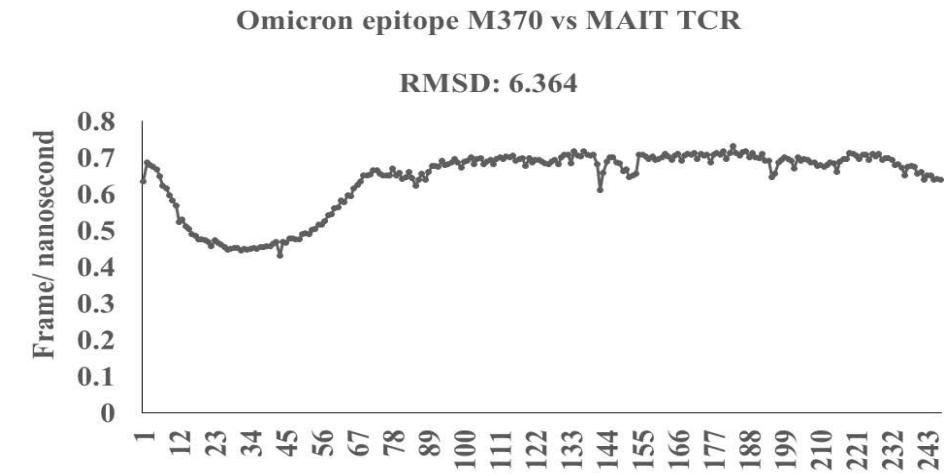


Fig.3H

Fig.3 A, B, C, D, E, F, G, H: Epitope peptides of Omicron variant (B.1.1.529) bind with mucosa-associated invariant T cell receptor (MAIT-TCR). The molecular docking and molecular dynamics experiments are performed to determine specific binding nature of Omicron epitopes and MAIT- TCR. The closest aligned atoms of amino acids within the cut off distance 2 Angstrom are determined by 10 cycle Molecular Dynamics alignment assay using the epitopes as mobile unit and MAIT-TCR is the target for none to one interaction. The root mean square deviation (RMSD, Angstrom) for each experiment between epitope peptide and MAIT-TCR demonstrate good fit alignment. The lesser RMSD, the better is the alignment thus represents better binding. The protein database files (PDB) are used in the experiments. (A) The molecular docking of Omicron variant Spike epitope (PDB: OM42) with MAIT-TCR (PDB: 4L9L). The interacting protein sequences are shown in a box at the top of the figure. The binding of OM42 by MAIT- TCR is shown in a box in the figure. (B) The molecular dynamics experiment demonstrates binding pattern of interacting atoms between OM42 (PDB) and MAIT-TCR (PDB: 4L9L). RMSD: 6.612 Angstrom. (C) The molecular docking of Omicron variant Spike epitope (PDB: OM60) with MAIT-TCR (PDB: 4L9L). The interacting protein sequences are shown in a box at the top of the figure. The binding of OM60 by MAIT-TCR is shown in a box in the figure. (D) The molecular dynamics experiment demonstrates binding pattern of interacting atoms between OM60 (PDB) and MAIT-TCR (PDB: 4L9L). RMSD: 7.282 Angstrom. The RMSD value shows comparatively less aligned amino acid sequences are present in OM60 epitope in the aspect of interaction with MAIT-TCR. (E) Molecular docking of Omicron variant Spike epitope (PDB: M312) with MAIT-TCR (PDB: 4L9L). The interacting protein sequences are shown in a box at the top of the figure. The binding zone of epitope peptide with MAIT-TCR is shown in a box in the figure. (F) The molecular dynamics experiment demonstrates binding of interacting atoms between M312 (PDB) and MAIT-TCR (PDB: 4L9L). RMSD: 6.131 Angstrom. (G) Molecular docking of Omicron variant Spike epitope (PDB:M370) with MAIT-TCR (PDB: 4L9L). The interacting protein sequences are shown in a box at the top of the figure. The binding of M370 by MAIT-TCR is shown in a box in the figure. (H) Molecular dynamics experiment demonstrates binding pattern of interacting atoms between epitope M370 (PDB) and MAIT-TCR (PDB: 4L9L). RMSD: 6.364 Angstrom. All these interaction events in the Molecular Dynamics experiments are based on oscillation atoms of interacting proteins defined at the rate of 30 frame per nanosecond for 100 nanosecond duration as described in Materials and Methods. All results are expressed as Frame per nanosecond versus Rendering time (nanosecond) at a particular executive root mean square deviation (RMSD) value. Statistical significance ($p<0.05$) of the frame per nanosecond values of experimental epitope peptides as compared with unrelated control peptide antigen85 with respect to MAIT-TCR has been determined by one factor ANOVA.

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
Control	42	35.47787	0.844711	0.00052
OM42	42	10.20515	0.24298	1.87E-05
OM60	42	25.81601	0.614667	0.006575
M312	42	3.844725	0.091541	4.45E-06
M370	42	21.48756	0.511609	0.006286

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	15.01255	4	3.753137	1399.918	1.5E-147	2.415694
Within Groups	0.549599	205	0.002681			
Total	15.56215	209				

Fig 3 (E- H) Statistical significance ($p < 0.05$) for binding and close atomic interactions was determined by one factor ANOVA between Frame per nanosecond (Angstrom) value of identified Omicron N terminal spike epitopes Spike epitopes and Control unrelated *Mycobacterium avium* antigen 85 peptide. Results obtained from Molecular Dynamics experiments (Fig 3E to H).

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A Prospective Cohort Study of Death Related to Opioid use in Older Patients with a Diagnosis of Cancer

By Hugo Moura de Albuquerque Melo, Jurema Telles de Oliveira Lima, Flávia Augusta de Orange, Maria Julia Gonçalves de Mello, Mirella Rebello Bezerra, Fabrício Oliveira Souto & José Luiz de Lima FIlho

Federal University of Pernambuco

Abstract- *Context:* Opioids use in older adults with cancer is growing, as do world population over 60 years of age.

Objectives: This study aimed to evaluate the association between the use of opioids and death in older patients with a cancer diagnosis.

Methods: We performed the analysis in a prospective cohort study with an internal comparison group. Statistical modeling considered clinical and laboratory variables. The cohort included 747 patients. Of these, 59 patients were using opioids, and they were selected to form the exposed group. Of the remaining 688, 59 were randomized to compose the group not exposed to opioids.

Keywords: *analgesics, opioid; fatal outcome; neoplasms, geriatric assessment.*

GJMR-K Classification: *DDC Code: 616.994061 LCC Code: RC262*

Strictly as per the compliance and regulations of:

A Prospective Cohort Study of Death Related to Opioid use in Older Patients with a Diagnosis of Cancer

Death Related to Opioid use in Older Patients with Cancer

Hugo Moura de Albuquerque Melo [α], Jurema Telles de Oliveira Lima [σ], Flávia Augusta de Orange [ρ], Maria Julia Gonçalves de Mello [ω], Mirella Rebello Bezerra [¥], Fabrício Oliveira Souto [§] & José Luiz de Lima FIlho [χ]

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Results: Opioid users were three times more likely to die and had a 3.69-fold greater chance of infection than those who did not use opioids. A normal score on the Mini Nutritional Assessment Short-Form reduced the chance of death by 73%, while a normal score on the overall standard Mini Nutrition Assessment score reduced the odds of death by 81%. The proposed statistical model reflects the high specificity of the correlation between death and opioid use.

Conclusion: In the group of older adults with cancer investigated, it can be inferred that there is evidence of association between clinical data, such as comorbidities and malnutrition, and mortality. This outcome was also reported when opioid use was associated with this population.

Keywords: analgesics, opioid; fatal outcome; neoplasms, geriatric assessment.

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I. Introduction

The world population over 60 years of age grows at a rate of 3% a year, being projected 1.4 billion by 2030 and 2.1 billion by 2050 and could reach 3.1 billion by 2100 [1]. These predictions in developing countries, such as Brazil, are occurring more intensely than in developed societies [2]. Aging must be seen, therefore, as one of the significant challenges of contemporary public health [3], and the management of the related complexity represents an increasingly common problem [4,5].

Age advancement is associated with a progressive decline in the functional reserve of multiple systems and a higher incidence of chronic-degenerative diseases, such as cancer, with age being the most critical risk factor for its advance. Cancer occurs more in people over 65 years of age than in younger patients. It is believed that an increase of approximately 70% in the number of new cases of cancer will occur in the next two decades [6-12].

For clinical evaluation of an elderly population with cancer, a comprehensive geriatric assessment (CGA) is recommended, using different instruments, basing the choice of the type of treatment and its contraindications on the profile of the patient. Among the symptomatic therapeutic options in older people with cancer are opioids for the treatment of pain or control of dyspnea [13-16].

Despite the beneficial results of opioids, these drugs can promote adverse effects [17], such as gastrointestinal symptoms (mainly constipation and nausea), dependence, analgesic tolerance, immunosuppression, and dysfunction in the intestinal barrier, leading to greater susceptibility to infections and impact on survival. Therefore, the use of these drugs has been related to death [17-22].

The objective of this study was to evaluate the association between the use of opioids and death in this geriatric population using statistical modeling, considering clinical and laboratory variables.

II. Materials and Methods

a) Design of the study

This was a prospective cohort study in older adults with a diagnosis of cancer, and we applied a group of internal comparisons. A total of 118 patients referred from 8 regional hospitals were included, attended from January 2015 to November 2017 at the Institute of Integral Medicine Professor Fernando Figueira (IMIP), a regional center of oncologic care.

Patients with skin cancer of the nonmetastatic basal cell or squamous cell carcinoma type and those who had undergone previous surgical treatment were excluded from follow-up. Patients were divided into two groups: exposed or not exposed to the use of opioids. Fifty-nine patients were exposed to opioid use, and the second group, nonexposed to opioid use, was composed of 59 patients.

This study was approved for execution by the Committee of Health Ethics of the Federal University of Pernambuco (CAEE: 00317118.4.0000.5208). The research was performed in accordance with relevant guidelines/regulations, and the informed consent was obtained from all participants.

b) Data collection

Data were collected according to the routine established at the Outpatient Clinic of Oncogeriatrics. After we evaluated their eligibility criteria and they signed the consent form, the patients were assessed by a multidisciplinary team consisting of a geriatrician, oncologist, nurse, physiotherapist, speech therapist, occupational therapist and physical educator. Sociodemographic, laboratory and clinical data were collected. According to the follow-up protocol, each participant was contacted by the team at least once a month during the follow-up period until the occurrence of death.

c) Variables analyzed

Exposure to opioids was defined as the recorded use of these drugs continuously since the first consultation in the outpatient clinic.

Death was defined as mortality occurred within any period after the date of entry into the study.

The demographic data selected were age gender, skin color, family status, schooling; smoking and use of alcohol.

Healthcare-associated infection was defined as any notification of an event with infectious characteristics, whether in an outpatient clinic or in a hospital environment, confirmed by laboratory tests and clinical history of the disease in the medical record.

Laboratory markers assessed were hemoglobin (12 to 17.4 g/dL), leukocytes (3.400 to 9.600 cells/mcL), and platelets (140,000 to 400,000/μL), which were considered abnormal when they were higher or lower than the normal ranges (in parentheses).

Tumor data included the primary topography (prostate, digestive system, breast, female gynecological system, urinary system, lung, and others) and metastatic disease (present or absent metastasis).

In the CGA performed for this study, the Charlson Comorbidity Index (CCI), the Karnofsky Performance Scale (KPS), the Mini-Mental State Examination (MMSE), the Geriatric Depression Scale (GDS-15), the Mini-Nutrition Assessment Short Form (MNA-SF) and the Mini-Nutritional Assessment (MNA) were used[23-30].

The changes in these instruments were analyzed as risk factors for the primary outcome, death. Data were considered in terms of normal or abnormal scores. Abnormal scores of the instruments were defined as CCI$\geq$ 2, KPS $\leq$ 50, GDS $\geq$ 5, MMSE $<$18 with no schooling and $<$24 with schooling, MNA-SF $<$12, and MNA$<$24. Patients with abnormal MNA-SF ($<$ 12) were submitted in a complementary way to the global MNA. The MNA score was stratified into patients at risk of malnutrition and malnourished (score $\leq$ 23.5) and those without nutritional risk ($\geq$ 24); patients with normal MNA-SF ($\geq$ 12) were considered as without nutritional risk.

d) Statistical analysis

To perform the bivariate analysis, the Pearson nonparametric chi-square test was used. The observed frequencies were obtained directly from the sample data, while the expected frequencies were calculated from these frequencies. The data were analyzed in the software R, version 3.5.0.

Considering death as the primary outcome and to find a function that could explain this variable response based on the other explanatory variables together, a model that is a particular case of generalized linear models has been proposed [31].

Duplication of information was withdrawn at data entry, and then we observed which variables directly affected the death/nondeath of the patient. Initially, all variables were included, and those that were not significant were removed one by one (according to which contributed least). After adjusting the model, it was necessary to observe if there were any flaws in its fit. For this, the diagnosis and residues of the proposed model were analyzed, and the quality (goodness) of the adjustment was analyzed to infer the predictive power of the model.

Once the proposed model was validated, its interpretation was based on the odds ratio function. This model was able to define the probability of death of the patients. Statistical modeling is used in predictive and explanatory studies in health research. When the dependent variable is binary (identifying whether an event occurs), the explanatory model includes a set of variables associated with a probability of event

occurrence (either as factors or as markers of protection or risk) [32].

Linear statistical modeling has become an essential tool in predictive and explanatory studies because of its ease of interpretation. In the formal structure of a linear model, each variable is multiplied by a coefficient, which, when standardized, directly measures the relative importance of the variable it accompanies [33].

For this study, it was considered that the dependent variable assumed only two values, 0 for nondeath and 1 for death, making this a Bernoulli variable [31]. It is also known that a repetition of 'successes' and 'failures' provides that Y (observation of the response-death variable) assumes a binomial distribution.

The model initially proposed is given by:

$$\log\left(\frac{\pi(\mathrm{X})}{1-\pi(\mathrm{X})}\right) = \eta,$$

in which:

X is the matrix of the values assumed by the explanatory variables; and

$\pi(\mathrm{x})$ is the probability that the patient will die due to the explanatory variables.

We can also write the model as follows:

$$\eta = \beta_0 + \beta_1 \mathrm{Opioid} + \beta_2 \mathrm{Infection} + \beta_3 \mathrm{Hemoglobin} + \beta_4 \mathrm{Leukocytes} + \beta_5 \mathrm{MNA\ Triage\ SF} + \beta_6 \mathrm{MNA\ Global\ Score}$$

III. Results

Table 1 presents the classification, operational definition, and categorization of sociodemographic and clinical-laboratory variables of the patients who used opioids and those who did not. Age, skin color and leukocyte count were significantly different between groups.

Looking at variables related to the tumor, Table 2 shows that approximately 40% of those who did not use opioids and 35% of those who used opioids had a tumor of the female genital tract. Moreover, approximately 91% of those who did not use opioids and 32% of those who used opioids had tumors in the process of metastasis. It was also observed that both the topography distribution of the tumors and the absence or presence of metastasis were significantly different between the groups that did not use opioids and those that used opioids.

Table 3 presents the classification, operational definition, and categorization of the variables related to the CGA. Similar behavior was observed between the two groups in the predominance of the CCI for the absence of comorbidities. The Charlson Index also showed that approximately 37% of patients using opioids had a high rate of comorbidities, compared to approximately 12% of those who did not use them, with a significant difference. In the evaluation of pain, approximately 47% of those who did not use opioids reported that they did not feel pain, and a similar percentage of patients who used opioids felt much pain, so the distribution of reported pain was significantly different between groups. According to the score of the MNA-SF, approximately 56% of users of opioids were malnourished, which was significantly higher than the nonuse group by the chi-square test. In the global score of the MNA, approximately 50% of those who did not use opioids and of those who did were classified as malnourished.

After that, we tabulated (Table 4) the classification, operational definition, and categorization of death by group. According to Table 4, approximately 75% of the opioid group died (p=0,0214), and 70% of deaths occurred within 180 days after the date of entry into the study. Among opioid users who died, the following tumor distributions were observed: gastrointestinal tract (36%), lung (25%), followed by others (16%), prostate (9%), female genital tract (7%), urinary system (4%) and breast (3%).

Table 5 presents the odds ratios of the variables in the model, along with their respective p-values and their standard errors. According to Table 5, the variables were statistically significant for the proposed model. It can be noted, as well, that users of opioids were three times more likely to die than those who did not use opioids; those who had an infection had 3.69 times the chance of dying of those who did not; those with abnormal leukocytes were 14 times as likely to die compared to those with normal leukocytes; and normal hemoglobin reduced by 67% the chance of death.

A normal score on the short form of the MNA reduced the chance of death by 73%, while a normal score on the global MNA reduced the odds of death by 81%. Based on these data, all variables were tested, and we selected those that allowed us to calculate the probability that a patient who used opioids died. This probability is given by:

$$\pi = \frac{e^{\beta_0+\beta_1 x_1+\beta_2 x_2+\beta_3 x_3+\beta_4 x_4}}{1+\ e^{\beta_0+\beta_1 x_1+\beta_2 x_2+\beta_3 x_3+\beta_4 x_4}}$$

$$\pi = \frac{e^{-2,8860\ +1,1268\ +1,3068+2,6531}}{1+\ e^{-2,8860\ +1,1268\ +1,3068\ +2,6531}} = \ 0{,}9003$$

Figure 1A shows the envelope graph, showing that the assumption that the response variable (death) assumed a binomial distribution was valid; that is, the frequency distribution of the data was adequate for the probability distribution.

The residues of Pearson were compared against the observations, that is, how well the observation was predicted by the model. There was a

random behavior of the residues, which confirmed the power of the model (Figure 1B).

Figure 1C shows the residues of the components of the deviation against the observations. It was observed that these residues also presented random behavior around zero and were concentrated within the limit of the specification, corroborating the validation of the proposed model. After performing the statistical analysis of the diagnosis, the predictive power of the model was assayed in the form of the area below the ROC curve.

According to Figure 1D, the area below the curve represented 85% coverage, reflecting the high specificity between death and use of opioids in the studied group under this model.

IV. Discussion

In this study, from a population of 748 patients from an outpatient clinic of oncogeriatrics, 118 were studied (59 exposed to the use of opioids and 59 nonexposed randomized patients) by comparing sociodemographic, laboratory, and clinical data to analyze the chance of death, with the use of opioids as an independent predictive factor influencing this outcome.

Among the sociodemographic variables, age and skin color reached statistical significance, as did leukometry in the laboratory analysis. The topography of the tumor and the existence of metastasis also yielded significant results in the analysis between the groups. It was interesting to note that among the nonopioid-exposed group, there was a higher frequency of older people, healthcare-associated infection, potentially more aggressive tumors, such as gastric and pulmonary tumors, and more patients with metastasis. These characteristics would be expected to be found more frequently in the group of opioid users, which in this study was the group that had the highest death rate, and that would supposed to be more fragile.

On the other hand, the CCI, the KPS, the pain variable of the QLQ-30, and the results of the MNA-SF were shown to be independent factors in the analysis between the groups of users and nonusers of opioids, suggesting a higher frequency with a statistical difference to the opioid group.

In studies conducted in older populations with cancer, in which a CGA was used, there was a positive correlation with mortality, in association with the presence of comorbidity and nutritional risk, as identified in our study. These data were reported in a systematic review by Yourman et al., which confirmed the association of comorbidities, with mortality in 6 to 12 months [34-37].

The CCI, used in our study, considers diagnoses and the severity of the clinical condition to reach a prognostic score for the patient. Due to the relevance of its results in association with unfavorable outcomes, such as mortality, its use in the older population with cancer is considered necessary because of the predictive power for the risk of death and, along with that, an indirect impact on the therapeutic decision [23; 38-41].

When discussing the evaluation of nutritional status, however, there are several descriptions of the association between the worst prognosis and mortality in research in older adults with cancer. When investigating a population older than 70 years with tumors in several sites, Soubeyran et al. found a three-fold greater chance of dying, as well as a low score in MNA, in its studied population, data compatible with those found in our sample. Martucci et al. corroborated the MNA-SF as a predictor of mortality in older adults with cancer, as suggested in our population [36, 37; 42-48].

In a retrospective cohort of 468 patients conducted by Edwards et al., there was a correlation of the KPS as a predictor of overall survival in older patients with cancer, as was also evidenced by Yourman et al., in line with the data we found. There is evidence, as well, that pain in older adults with cancer, when it interferes with routine and quality of life, is seen as arisk factor for mortality. It thus seems that there is a basis for the association between the prediction of mortality and the geriatric evaluations analyzed [36, 49]. However, in the search for the association between the outcome of death and the use of opioids, there is still discordant information [50, 51]. In the present study, we found three times the chance of death in opioid users compared to those who did not use opioids. It was noticed, with the construction of a statistical model, that there was a high association between death as the primary outcome and the use of opioids, reaching 85% specificity in the prediction of death, according to the analysis of the ROC curve.

In a retrospective cohort of 50.658 patients on Tennessee Medicaid, the use of opioids in patients with nononcologic pain was associated with high rates of outpatient mortality (115/10.000 patient-years among users of morphine) for causes other than overdose. This finding was corroborated by the study of Ray et al., which showed a 1.64-fold increased risk for all-cause mortality for patients on chronic therapy with an opioid compared to those who underwent analgesia with anticonvulsants or a low dose of antidepressant [52, 53].

In contrast, a retrospective study that investigated the association between survival and prescription of opioids in a total of 17.202 individuals, found that the prescription rate of opioids was 1.22 times higher among oncologic survivors than in controls without a diagnosis of cancer [50].

We discussed that there is an association reported in the scientific literature between mortality and

prognostic indicators used in CGA, such as comorbidities (CCI), performance status (KPS), and malnutrition (MNA), and between opioid use and mortality. In this context, our study is the first one of which we are aware to accurately infer in the older population with cancer that the use of an opioid is a predictor of mortality, establishing a correlation between these data unifying the associations to death in the same studied population.

Among the patients investigated, we also identified that those who had an infection had 3.69 times the chance of dying of uninfected patients among users of opioids. Cumulative studies have shown that treatment with opioids may be associated with many negative pathophysiological consequences, including respiratory depression, immunosuppression, constipation, and a loss of homeostasis and intestinal barrier, increasing the risk of sepsis [18-22, 55, 56].

Consistent with prior laboratory studies, there is a recent analysis suggesting that septic patients treated with opioids have increased mortality rates compared to those not treated with opioids (mortality within 28 days of 10.35% for patients treated with opioids versus 2.4% for those not treated, with $p < 0.001$ after adjustment for various confounding factors) [55-58].

It is known that among these patients, higher pain is correlated with lower quality of life and that pain, per se, is already associated with increased mortality. Thus, there is no benefit in avoiding opioids in the context of moderate to severe pain. In contrast, there is a high prevalence of pain in oncology patients and the older population, and abandoning the effectiveness of pain control provided by the use of opioids, without an equivalent replacement, is both inhumane and deleterious, given the very significant adverse effect of pain and stress on the progression of cancer [22; 50; 59; 60].

It is also important to note that our group of patients, with a high degree of comorbidity (high ICC), low functionality (KPS <50) and malnourished (by MNA-SF), represents a group of older adults in frail condition. In these cases, deprescription is a fundamental practice aiming to reduce polypharmacy and the side effects of drugs by expunging nonfundamental drugs. This reasoning does not necessarily exclude opioids but those drugs that, when combined, have a high risk of death [61-63].

This study has the strengths of a longitudinal cohort, in which the patients who composed the samples were referred from 8 regional centers, from Pernambuco state in Northeast Brazil, to a specialized outpatient clinic in a teaching hospital of significant size. The nonexposed group was randomized and matched to the group exposed in the analysis. An individual follow-up was performed, and changes or variations in the characteristics of the participants were controlled so that the analytical method was rigorously applied in the longitudinal interpretation of the data. The scales used in CGA are all validated and used internationally.

However, it was an exploratory study with a heterogeneous population of older patients with cancer, with several histological diagnoses. The associations found should be confirmed for specific tumor groups and in other populations. There was no control or standardization of the type of opioid or the dose, only the determination in the first consultation that the patient had taken some opioid drug continuously. In addition, the studied group had characteristics that exposed it to the depletion of immunity, such as the presence of cancer per se and older age, which already introduces a higher chance of death [18, 22, 49, 62].

V. Conclusion

In the group of older adults with cancer investigated, it can be inferred that there is evidence of association between clinical data, such as comorbidities and malnutrition, and mortality. This outcome was also reported when opioid use was associated with this population. Therefore, it is suggested the practice of responsible deprescription, in the case of older adult patients, when association between factors related to frailty (such as malnutrition and comorbidities) and polypharmacy and, always, stimulate safe prescribing, because opioids are fundamental medications for the quality-of-life of those in pain and their safe use should continue to be encouraged, when it is the best therapeutic alternative.

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Conflicts of Interest

No conflicts of interest to declare.

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Table 1: Classification, operational definition, and categorization of sociodemographic and clinical-laboratory variables

		Nonuse of opioids		Use of opioids		P-value
		n	%	n	%	
Age	60 - 70	12	20,34	33	55,93	0,0002
	71 - more	47	79,66	26	44,07	
Gender	Male	27	45,76	31	52,54	0,5807
	Female	32	54,24	28	47,46	
Skin Color	White	12	20,34	31	52,54	< 0,0001
	Nonwhite	47	79,66	28	47,46	

Living with a partner	With partner	22	37,29	31	52,54	0,0957
	Without partner	37	62,71	28	47,46	
Schooling	Up to 4 years	47	79,66	41	69,49	0,2046
	More than 4 years	12	20,34	18	30,51	
Smoking	Yes	2	3,39	3	5,08	1,0000
	No	57	96,61	56	94,92	
Alcohol misuse	Yes	25	42,37	34	57,63	0,1408
	No	34	57,63	25	42,37	
Healthcare-associated infection	Yes	43	72,88	32	54,24	0,0558
	No	16	27,12	27	45,76	
Hemoglobin	Normal	26	44,07	36	61,02	0,0971
	Anemia	33	55,93	23	38,98	
Leukocytes	Normal	56	94,92	42	71,19	0,0014
	Abnormal	3	5,08	17	28,81	
Platelets	Normal	51	86,44	44	74,58	0,1632
	Abnormal	8	13,56	15	25,42	

Table 2: Variables related to the tumor

		Nonuse of opioids		Use of opioids		P-value
		n	%	n	%	
Topography of the tumor (ICD 10)	Prostate	6	10,17	2	3,39	0,0053
	Gastrointestinal tract	12	20,34	6	10,17	
	Breast	2	3,39	17	28,81	
	Female genital tract	24	40,68	21	35,59	
	Urinary System	3	5,08	2	3,39	
	Lung	8	13,56	4	6,78	
	Others	4	6,78	7	11,86	
Metastasis	Absence	5	8,47	19	32,20	0,0029
	Presence	54	91,53	40	67,80	

ICD 10 – International Classification of Diseases, Version 10.

Table 3: Classification, operational definition and categorization of variables related to CGA

		Nonuse of opioids		Use of opioid		P-value
		n	%	n	%	
Charlson Comorbidity Index (CCI)	Absence	45	76,27	35	59,32	0,0028
	Low	7	11,86	2	3,39	
	High	7	11,86	22	37,29	
Karnofsky Performance Scale (KPS)	≤ 50	7	11,86	23	38,98	0,0015
	>50	52	88,14	36	61,02	
Scale of the abbreviated Geriatric Depression (GDS-15)	Normal	2	3,39	8	13,56	0,1011
	Low	41	69,49	33	55,93	
	Medium/High	16	27,12	18	30,51	
Score of the Mini Mental State Examination (MMSE)	Normal	27	45,76	27	45,76	0,8706
	Medium	20	33,90	22	37,29	
	Severe	12	20,34	10	16,95	

Assessment of pain, from the scale of quality of life (QLQ-30 of the EORTC)	No pain	26	44,07	5	8,47	< 0,0001
	Few pain	8	13,56	9	15,25	
	Moderate pain	16	27,12	19	32,20	
	Much pain	9	15,25	26	44,07	
Score of the Short Form of the Mini Nutritional Assessment (MNA-SF)	Normal	24	40,68	12	20,34	0,0027
	Risk of malnutrition	20	33,90	14	23,73	
	Malnourished	15	25,42	33	55,93	
Global score of the Mini Nutritional Assessment (MNA)	Normal	30	50,85	29	49,15	0,1069
	Risk of malnutrition	25	42,37	30	50,85	
	Malnourished	4	6,78	0	0,00	

CGA – Comprehensive Geriatric Assessment

QLQ 30 – Quality of Life Questionnaire

EORTC – European Organization for Research and Treatment of Cancer

Table 4: Classification, operational definition, and categorization of the most severe adverse event (outcome) – death.

		Nonuse of opioids		Use of opioids		p-value
		n	%	n	%	
Death	Yes	20	33,90	44	74,58	0,0214
	No	39	66,10	15	25,42	
Death within 180 days	Yes	11	55,00	31	70,45	0,3562
	No	9	15,25	13	29,55	
Death between 180 and 360 days	Yes	4	6,78	7	15,91	0,7806
	No	16	27,12	37	84,09	
Death more than 360 days	Yes	5	8,47	6	13,64	0,4476
	No	15	25,42	38	86,36	

Table 5: Estimates of the parameters and significance of the variables selected in the model to explain the probability of a patient who uses opioid to die.

Coefficients	Odds	Standard error	Pr(>|z|)
Intercepted	0,0558	1,4215	0,0423
Opioid	3,0858	0,4804	0,0190
Infection	3,6943	0,5140	0,0110
Hemoglobin	0,3243	0,5093	0,0270
Leukocytes	14,1980	1,1140	0,0172
MNA Triage SF	0,2657	0,5339	0,0131
MNA Global Score	0,1845	0,9030	0,0612

MNA – Mini Nutritional Assessment

SF – Short Form

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Bowel Obstruction Due to Meckel's Diverticulum: A Case Report

By Mounir Bouali, Kenza Benjelloun Touimi, Abdelilah El Bakouri, Khalid El Hattabi, Fatim-Zahra Bensardi & Abdelaziz Fadil

Abstract- Meckel's diverticulum is the most prevalent congenital abnormality of the gastrointestinal tract. This anomaly is due to the incomplete obliteration of the omphalomesenteric duct during the 7th week of gestation and is classically located 2 feet proximal to the ileocecal valve (1).

While most of the population may be asymptomatic, clinical manifestation, including gastrointestinal bleed and intestinal obstruction, can emerge. Despite the frequency of Meckel's diverticulum, it is commonly misdiagnosed due to its mimicry of appendicitis. We reported in our case a patient with bowel obstruction.

Meckel's divertiulum was discovered during surgery.

Keywords: meckel's diverticulum, bowel obstruction.

GJMR-K Classification: NLMC Code: WI420

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Keywords: meckel's diverticulum, bowel obstruction.

I. Introduction

Meckel's diverticulum is the most common congenital malformation of the gastrointestinal tract.

Due to the rarity of cases in adults, it is still misdiagnosed preoperatively.

We describe in our case a patient with bowel obstruction due to meckel's diverticulum.

II. Case Presentation

Patient was 41-year-old man.

He had no medical history.

He was referred to our emergency, he had symptoms of intestinal obstruction: he couldn't have a pass gas, he noticed stomach pain and a swollen belly.

He had no external gastrointestinal bleeding.

On examination, he was afebrile, with normal respiratory rate and normal resting heart rate.

On physical exam, the patient's abdomen was distended, tympanic on percussion.

Digital rectal exam was normal with no hematochezia.

Abdominal CT scann showed small and large bowel distention with a caliber disparity in the right iliac fossa and air-fluid levels.

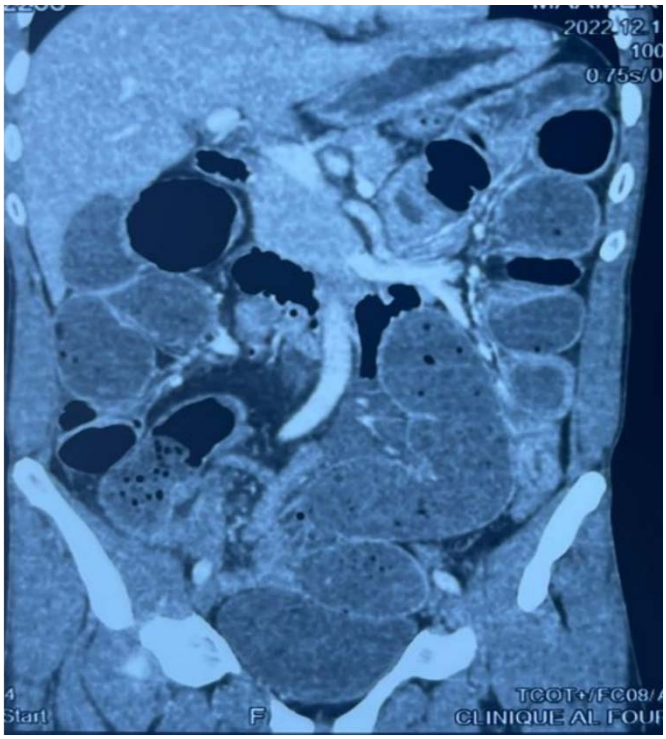

Figure 1: Caliber disparity in the right iliacfossa

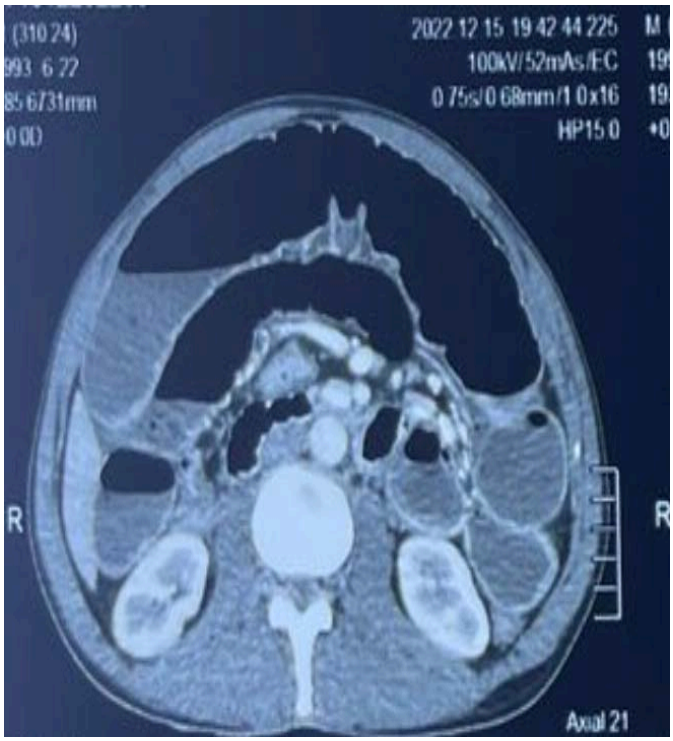

Figure 2: Air-fluid levels

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On the same admission day, the patient was transferred to the operating room.

The patient and his family gave their approval to do surgery.

During laparotomy under general anesthesia, the exploration showed a meckel's diverticulum adhering to the abdominal wall, located at 60 cm from the ileocecal valve responsible for a small bowel volvulus which is the site of perforative lesions and also responsible for distension of the small bowel measuring 5 cm.

We proceeded to 10 cm small bowel resection carrying a Meckel's diverticulum and perforative lesions and end to end bowel anastomosis.

The post-operative care was simple, he was discharged from hospital on postoperative day 5, after allowing liquid feeding without incident.

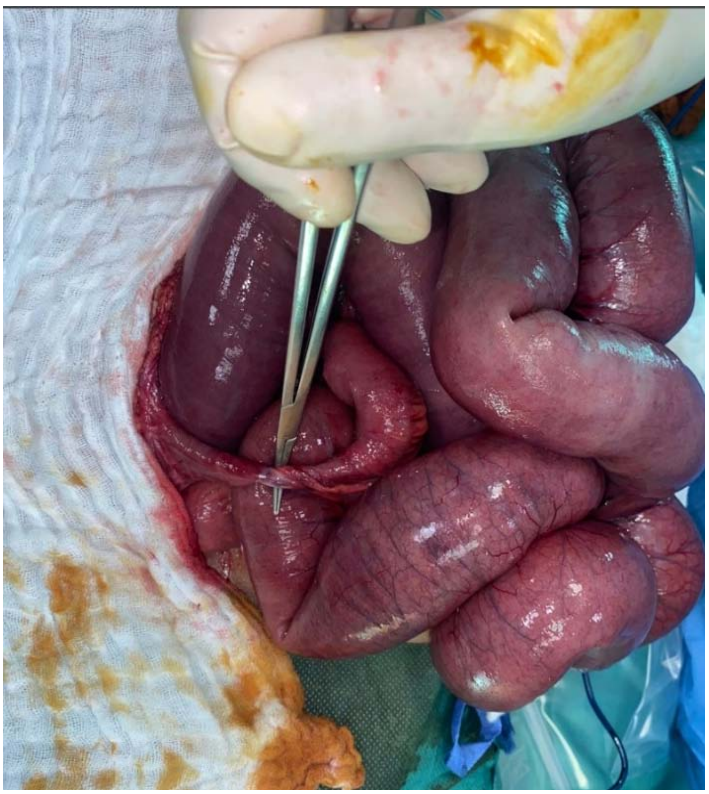

Figure 3: Meckel's diverticulum adhering to the abdominal wall

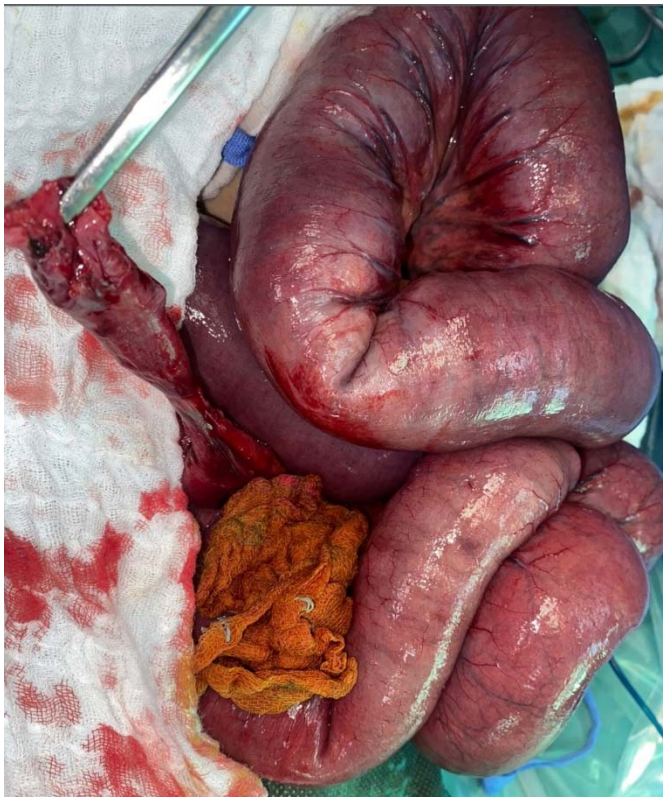

Figure 4: Meckel's diverticulum becoming free

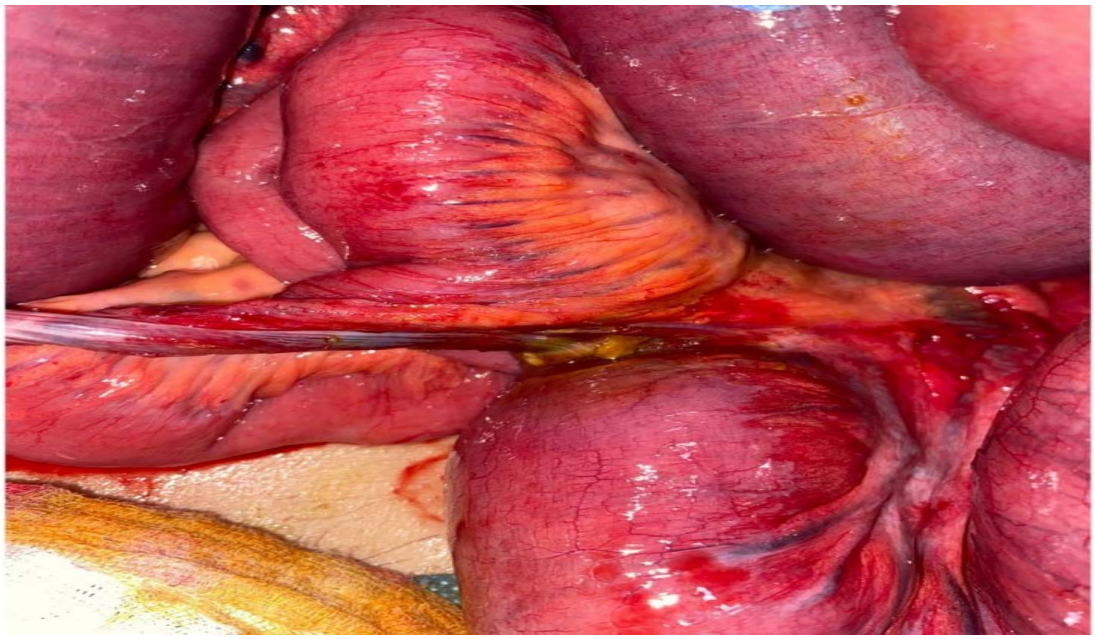

Figure 5: A. Meckel's diverticulum-B. perforative lesions

III. Discussion

Meckel's diverticulum was named after Johann Friedrich Meckel, who described its anatomy and embryology in 1809 (2).

This anomaly is due to the incomplete obliteration of the omphalomesenteric duct during the 7th week of gestation and is classically located 2 feet proximal to the ileocecal valve (1).

Meckel's diverticula are lined with heterotopic mucosa in up to 60% of cases in the following manner: gastric mucosa, 62%; pancreatic, 6%; both gastric and pancreatic, 5%, jejunal, 2%; Brunner's glands, 2%; and gastric and duodenal, 2% (3).
Most of the population may be asymptomatic.

Bleeding from Meckel's diverticulum due to ectopic gastric mucosa is the most common clinical presentation, especially in younger patient, but it is rare

in the adult population. The complications in adults include: obstruction; intussusception; ulceration; haemorrhage; and, rarely, vesicodiverticular fistulae and tumours (4).

The diverticulum is occasionally identified incidentally on imaging studies and may be found during the course of a laparotomy performed for other reasons. The preferred diagnostic method is laparoscopy in doubtful cases. However, laparoscopy is not an initial step of diagnostic modalities as it is more invasive compared to conventional imaging methods (5).

Plain X-ray, barium studies and computed tomography (CT) scans are seldom beneficial for a preoperative diagnosis of the diverticulum. The typical appearance of an intestinal obstruction may be demonstrated by plain abdominal radiographs. When distension develops in a diverticulum, diagnosis may be established due to a gas-filled viscous appearance in the right iliac fossa or middle abdomen region. If a perforation develops as a complication, the findings of pneumoperitoneum may be seen on upright chest and plain abdominal radiographs. Characteristically, the diverticulum is delineated as a contrast-filled out pouching which has a junctional fold pattern and is seated on the anti-mesenteric margin of the small bowel (5).

Ultrasonography, although not specific enough for imaging this condition, may reveal a tubular diverticulum swollen with fluid in a region away from the cecum, invagination, segmental thickening of the bowel walls, swelling of diverticular wall and pelvic abscess (6).

Capsule endoscopy is a novel technological tool for the examination of the small bowel in a noninvasive and simple manner. It has been proved in a number of studies that capsule endoscopy has the capability to detect small intestine lesions in cases with obscure gastrointestinal hemorrhage. The entire small intestine can be examined by both double-baloon enteroscopy and capsule endoscopy. For the detection of hemorrhagic lesions in the small bowel, other studies proved that the efficacy of both capsule endoscopy and double-baloon enteroscopy is similar. However, capsule endoscopy is contra-indicated and also difficult in cases under ten years of age. Furthermore, it is relatively simple to reach via the retrograde double-balloon enteroscopy method, as the distance of the Meckel's diverticulum is generally closer than a meter from the ileocecal valve (7).

The treatment for Meckel's diverticula is shown in this algorithm (8):

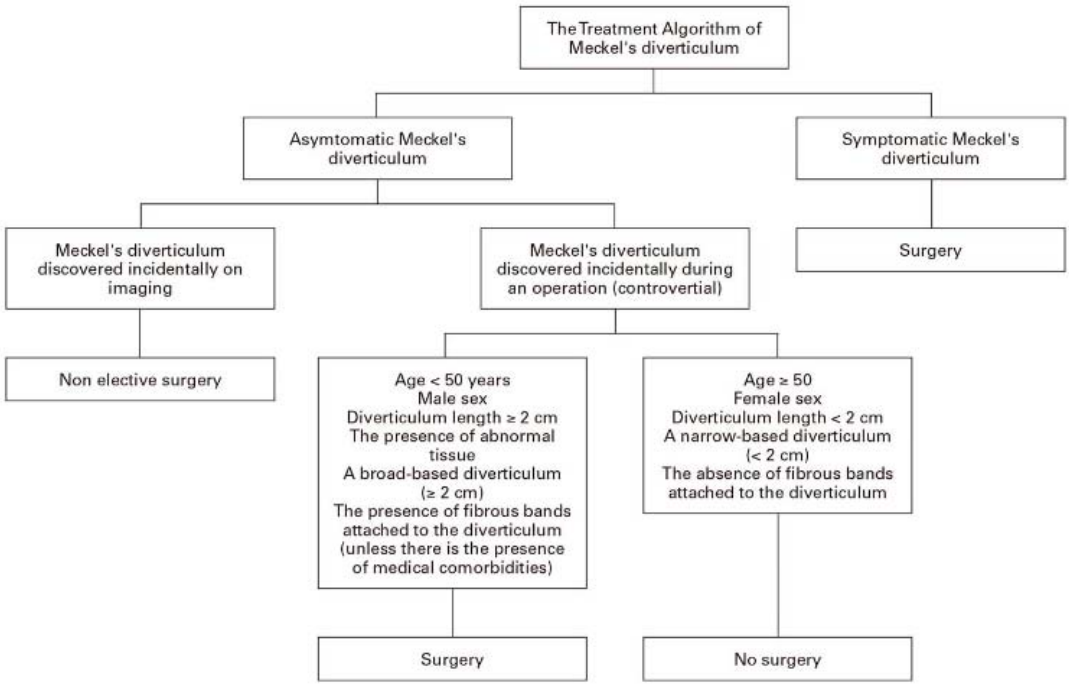

Figure 6: The treatment algorithm of Meckel's diverticulum

IV. Conclusion

Meckel's diverticulum is the most prevalent congenital abnormality of the gastrointestinal tract.

Most of the population may be asymptomatic.

A good level of knowledge of the clinical, embryological, radiological and pathological features of Meckel's diverticulum will enable a rapid and proper diagnosis of patients, thereby allowing treatment via a timely surgical intervention.

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The Effect of Anxiety on Sleep Quality among COVID-19 Survivors in Barangay North Bay Boulevard South of Navotas City

By Fraulein P. Tormon, Jaymee Marie C. Torres, Celestine Rio A. Tameta, Rehama Eshrak A. Tan, Sarah Tiffany A. Tangpos, Andreanina C. Tapiz, Mary Wincel B. Tenorio, Lorefel C. Tibus, Jereko C. Toreja, Mark Johben C. Toreja & Charlene B. Tuazon

Abstract- Background: The outbreak of COVID-19 has impacted the mental health of the people. The study purpose is to look into the different factors or levels of anxiety that influence the sleep quality of a COVID-19 survivor in Barangay North Bay Boulevard South of Navotas City.

Objectives: This study aimed to investigate the effect of anxiety on sleep quality of COVID-19 survivors in Barangay North Bay Boulevard South of Navotas City.

Materials and Methods: In this cross-sectional study, data were collected between May 7, 2022 to May 25, 2022. The total population is 1891 with a sample size of 336. Informed consent form, GAD7 and Pittsburgh sleep quality index questionnaire were used as data collection tools.

Keywords: *anxiety; sleep quality; COVID-19.*

GJMR-K Classification: *DDC Code: 813.54 LCC Code: PS3561.I483*

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Results: In the relationship of anxiety to age, with the P Value of 0.001 indicates that age greatly influenced the development of anxiety among COVID-19 survivors as it consistently had a statistically significant result all throughout the age groups. In consideration of Sleep quality in regards to age, it shows that it is highly influenced and is statistically significant with the score of 0.022 to 0.001 which indicates that the age of the people who were positive and the deterioration of their sleep quality rises as they grow older. Both variables in relation to gender showed no statistical significance.

Conclusion: Our study implies that gender is insignificant in both anxiety and sleep quality. As for age, it showed strong evidence that sleep quality and the development of anxiety among COVID-19 survivors are greatly influenced by different age groups.

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Keywords: anxiety; sleep quality; COVID-19.

I. Introduction

COVID-19 was first reported on December 31, 2019, by the Chinese authorities to the World Health Organization as initial pneumonia cases of unknown origin in Wuhan City. In the following month of the year 2020, it was globally announced acknowledging the number of cases surpassed 90 million. Consequently, a variety of issues arose, including the increase in the intensity and level of anxiety which has an impact on a person's physical activities, particularly the primary physiological critical need for sleep (Morin et al., 2020). Moreover, human anxiety was heightened by several factors such as the fast transmission of the virus, mortality caused by the infection, lack of knowledge on the management and treatment, social isolation, disturbance of daily routine, and uncertainties. Unfortunately, even COVID-19 survivors continue to have their usual body cycles interrupted.

Some studies have linked COVID-19 pandemic to the changes in an individual's various physiological needs like food, shelter, and sleep, which subsequently destabilized those at the top of the hierarchy of needs, exacerbating the negative consequence among individuals infected with COVID-19 (Ryan et al., 2020). Additionally, another important negative effect of COVID-19 outbreak is the deterioration of sleep quality, consisting of sleep delay, sleep duration, habitual sleep efficacy, sleep disorders, use of sleeping medication and daytime dysfunction that expresses the individual's sleep efficacy. Clearly, it implies that anxiety can worsen sleep quality. Furthermore, one of the psychological effects of COVID-19 that could occur are sleep disturbances.

Overtime, anxiety evolves and aggravates other physical or mental health conditions of the person depending on the duration of the negative stimulus or stressors they experienced (Généreux et al., 2020). These circumstances at hand are currently unavoidable as the pandemic shows an unknown time on when it will end. This study aims to find out the effect of anxiety to

sleep quality based on the respondents age and gender. This study will compare the mean and standard deviation of the result from the test that measures anxiety level and sleep quality level. The scores that will be gathered from these tests will be analyzed for their relationship to the gender and age of the respondents with the use of two-tailed T Test for Gender and one way ANOVA for the age. Lastly, both variables will be tested for relationship using Pearson R to see if both will have parallel effects interchangeably.

II. Methodology

a) Study Design

In this study, the researchers utilized a cross-sectional procedure, explanatory research study design. First, the researchers examined the specific sleep quality of the participants. Second, the researchers correlated the sleep quality to the level of anxiety among demographics of age and gender. Third, the researchers correlated the relationship between the generalized anxiety and sleep quality among the COVID-19 survivors brought about by the pandemic. Lastly, the researchers used self-report measures which may be affected by social desirability bias. All questionnaires were strictly standardized and GAD7 and PSQi questionnaires were used. In addition, each of the questionnaires has a specific checklist in line with the effect of anxiety of a COVID-19 survivor and the sleep quality wherein these variables were also present in the research study. Detailed posters which included the information regarding the study were also provided prior to the interview proper.

b) Sample Size Computation

In the present study, the standard formula was used for determining the sample size of a known population. The confidence level was 90% (z-score of 1.645) with a default standard deviation of 50% (0.5) and margin of error of 10% (0.10). Starting with a total population of 1891, using the standard formula, it was then computed to 330 sample size which will represent the total population. This study utilized a Judgment or Purposive sampling technique. A non-probability sampling method that fits best in the type of population of this research was used as each chosen participant relies on the judgment of the researchers if they can meet the specific characteristics to participate in the study. The researcher was guided by a barangay official in gathering data in the target population.

c) Inclusion and Exclusion Criteria

As part of the inclusion criteria, the target population that partake in the research are Filipino male or female adults whose age ranges from 21-73 years old residing in North Bay Boulevard South of Navotas, Metro Manila. Participants are COVID-19 patient survivors who are able to comprehend the standardized questionnaire that is provided by the researchers. As part of the exclusion criteria, any person with clinical impairment such as motor, sensorial, or intellectual disability or illiteracy that may prevent answering the questionnaire as well as acute and chronic conditions that would limit the ability of the respondent to participate. Refusal to give informed consent is respected and will not be forced to partake in the study.

d) Interventions and Data Collection

The assigned researchers in data collection followed two types of manner of survey dissemination yet retains the process of purposive sampling; The total number of population is 1891 with a sample size of 336. The researchers utilized a well-ventilated room provided by the aid of the clinic which is coordinated with the barangay where the participants are the consented patients who are previously contracted with COVID-19. The time of administration depends on the day's clinic hours. The test administration consists of one consent form and two standardized tests, with a duration of 5 to 10 minutes each session. Throughout the administration of the test is accompanied by the assigned member of the barangay who stands as witness and confirms the record of the participant whether he or she has a history of contracting COVID-19. The other manner of survey dissemination is when it is outside the clinic hours. The researchers along with the assigned coordinator of the barangay surveys the specific locale and visits the address of covid survivors under the record list provided by the barangay coordinator. The process of administration in this method remains the same with the one in the clinic which the researchers assure that there is consent and secures the data's integrity by avoiding extraneous variables that could affect the data collection.

e) Measurement of Outcome and Data/ Statistical Analysis

The researchers utilized excell application to tally and arrange the raw data collected which is then forwarded to the statistician who used SPSS software to calculate the mean, correlation, two tailed T test, One way ANOVA, Pearson R, Chi square and other statistical operations.

III. Results

Table 1: Demographic Profile of the Respondents

Respondents Characteristics	Number (n)	Percentage (%)
Gender		
• Male	125	37.20%
• Female	211	62.80%
Age		
• Adult (21 - 34)	39	11.61%
• Early Middle Age (35 - 49)	143	42.56%
• Middle Age (50 - 65)	131	38.99%
• Elderly (>66)	23	6.85%

Table 1 Presents the frequency of distribution for each respondent based on their gender and age. As for the gender, it comprises 211 female respondents which makes up 62.80% of the total sample size in comparison to 125 male respondents which makes up for 37.20% of the total respondents. As for the distribution of respondents in consideration to Age it can be seen that most respondents are aged 35 - 49 comprises the most percentage of respondents, followed by ages 50 - 65 and 21 - 34 as well as those greater than 66 respectively.

Table 2: Mean score of Anxiety and Sleep Quality with Standard Deviation by Gender and Age

	Gender		Age			
	Male	Female	21-34	35-49	50-65	>66
Mean Score of Anxiety	9.92	9.63	1.07	11.37	9.04	18.21
Standard Deviation	5.40	5.32	1.22	2.42	5.33	1.88
Mean Score of Sleep Quality	9.03	9.09	7.46	9.49	7.54	17.87
Standard Deviation	4.65	4.24	3.02	2.77	4.69	0.34

Table 2 presents the summarization of data for the scores on Anxiety in relation by gender and age, the total mean score of anxiety for the male is 9.92 with a standard deviation of 5.40 which falls under the category of mild level of anxiety as well as for the female gender which scored a mean of 9.63 with a standard deviation of 5.32 which falls to mild category as well. As for the age, the score for the respondents aged 21-34, falls under the category of Minimal Anxiety, both ages 35-49 and 50-65 falls under the category of moderate Anxiety and lastly for those >66 scored a mean of 18.21 which falls under the severe level of Anxiety.

Table 2 also presents the summarization of data for the sleep quality in relation by gender and age, both genders male and female showed not much of differences which is 9.03 and 9.09 which both fall under moderate Sleep Disturbance, with a standard deviation of 4.65 and 4.24 respectively. As for the age, it became apparent that ages 21 - 34 and 50 - 65 show similarity in their level of sleep disturbances which are both mild. As for ages 35 - 49 it showed to be that of moderate sleep disturbance with a score of 9.49. Lastly, those who are aged >66 with a mean of 17.87 which falls under the category of severe sleep disturbances shows that the elderly are heavily affected during pandemic.

Table 3a: Comparison of the Mean and Standard Deviation of Anxiety as to Gender

Gender	Mean of Anxiety	Standard Deviation	Two-Tailed T Test
Male	9.92	5.40	.900
Female	9.63	5.32	.902

Table 3b: Comparison of the Mean and Standard Deviation of Anxiety as to Age

Age	Mean of Anxiety	Standard Deviation	One way ANOVA
Adult (21 - 34)	1.07	1.22	0.001
Early Middle Age (35-49)	11.37	2.42	0.001
Middle Age (50-65)	9.04	5.33	0.001
Elderly (>66)	18.21	1.88	0.001

Table 3a presents both the result of correlation between gender and age in regards to anxiety. For the anxiety in relation to gender, it showed no significant relationship which shows that no gender is heavily affected but rather both suffer the effects of anxiety during the pandemic. As for the Table 3b it shows a very significant relationship all throughout the different age groups having a p value of 0.001

Table 4a: Comparison of the Mean and Standard Deviation of Sleep Quality as to Gender

Gender	Mean of Sleep Quality	Standard Deviation	Two-Tailed T Test
Male	9.03	4.65	0.942
Female	9.09	4.24	0.942

Table 4b: Comparison of the Mean and Standard Deviation of Sleep Quality as to Age

Age	Mean of Sleep Quality	Standard Deviation	One way ANOVA
Adult (21 - 34)	7.46	3.02	0.022
Early Middle Age (35-49)	9.49	2.77	0.022
Middle Age (50-65)	7.54	4.69	0.001
Elderly (>66)	17.87	0.34	0.001

Table 4a presents the computed p value for the gender in regards to sleep quality which shows insignificant findings as well, it shows that there were no strong indications of it being a significant statistical value.

As for Table 4b it consistently shows significant statistical result with a value P value of <0.05 all throughout the age groups indicates that it has strong evidence that sleep quality is greatly influenced by age.

Table 5: Correlation of the Mean and Standard Deviation of Anxiety and Sleep Quality

Variable	Mean	Standard Deviation	Pearson R
Anxiety	2.62	0.89	0.604
Sleep Quality	1.66	0.70	0.604

Table 5 presents the correlation between variables with a value of 0.604 which falls under the category of moderate positive correlation which is an ideal outcome in order to confirm the hypothesis and

indicate that both variables are connected and were greatly influenced during the pandemic.

IV. Discussion

Based on the statistical analysis utilizing Two tailed T Test, One way ANOVA, Pearson R and Chi Square, relating both variables to the demographic profile of the respondents, there were many statistically significant findings that were found. It can also be concluded that there is statistically significant evidence that can reject the null hypothesis with the computed score of 0.604 using Pearson R signifies that both variables affect each other interchangeably those who had the COVID-19 and is a survivor even up to this day.

In the case of anxiety in relation to gender, it was found out that it is statistically non-significant with a score of .900 and .904 which are both higher than the targeted P Value of 0.05, thus it can be said that gender does not play a role or influence with great significance the development of anxiety in addition to the respondents being COVID-19 survivors. In the case of the relationship of anxiety to age, it can be concluded based on the data gathered with the P Value of 0.001 that age greatly influences the development of anxiety among COVID-19 survivors. It consistently had a statistically significant result that indicates the importance of age consideration when studying the impact of the pandemic to those who had contracted and is of old age. In an existing research on the mental health burden in China during the COVID-19 outbreak, there was no difference between genders in the prevalence of generalized anxiety symptoms, however younger persons reported higher anxiety symptoms (Bäuerle, A. et al., 2020).

In consideration of sleep quality with regards to gender, it was found that yet again it yielded no statistically significant result with the score of 0.942, thus can be concluded that both genders are equally affected by disturbances to the quality of sleep of those who had COVID-19 during the pandemic. It signifies that the biological identity does not greatly influence the deterioration of sleep quality of those who had been infected. As for the sleep quality in relation to age, it shows that it is highly influenced and is statistically significant with the score of 0.022 to 0.001, indicating that by the age of the people who were positive and the deterioration of their sleep quality rises as they grow older. Data from a cross-sectional study, showed that there was no statistically significant association between gender and age as a factor for sleep disturbance (Gupta, B. et al., 2020). Therefore, it is likely that the effects of gender and age on sleep quality among COVID-19 survivors are complicated and contradictory, and that some social-psychological factors may interact. As for the limitations of our study, it can be said that although the study was concluded to be statistically significant as supported by the analysis of data, many can still be added in order to cover more areas and consider more criteria for future research to be made. One of the limitations faced during the making of the research is the time in which the targeted response is of long overdue, relying on the ability of the respondents to recall their experiences during the pandemic heavily affected the study. During research, it is time constricted as well, making cross sectional studies have a lesser impact in comparison to other studies, but it could prove to have more fruitful results if given enough time to do so.

V. Conclusion/recommendations

In conclusion, our study provided informative data to determine the effect of anxiety on sleep quality among COVID-19 survivors in Barangay North Bay Boulevard South of Navotas City. Our findings imply that sleep quality in relation to gender showed few differences which both fall under moderate sleep disturbance. Both genders are equally affected by disturbances to the quality of sleep of those who had COVID-19 during the pandemic. It signifies that the biological identity does not greatly influence the deterioration of sleep quality of those who have been positively infected. While for the relationship of age on sleep quality, it showed strong evidence that sleep quality is greatly influenced by age. The elderly were more affected and experienced severe sleep disturbances during the pandemic. It shows that it is highly influenced by the age of the people who were positive and that the deterioration of their sleep quality rises as they grow older. For the anxiety in relation to gender, it showed no significant relationship, which shows that no gender is heavily affected but rather both suffer the effects of anxiety during the pandemic. Gender does not play a role or influence with great significance the development of anxiety, in addition to the respondents being COVID-19 survivors. While for the relationship of anxiety to age, it shows a very significant relationship throughout the different age groups. Age greatly influenced the development of anxiety among COVID-19 survivors; it consistently had a significant result.

For future recommendations, evidenced-based psychological interventions may be useful when considering suitable interventions for anxiety among COVID-19 survivors. Both low-intensity intervention with self-help approaches and high-intensity psychotherapy can be used as evidenced-based interventions. We could also employ past strategies like confidence building, distribution of informational pamphlets, describing signs and support resources for anxiety, as well as availability of sessions and confidential telephone support with psychiatric staff. As for the sleep outcomes, especially for the elderly, adequate care,

emotional support, and motivation should be given by their family.

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Association between Necrotizing Sialometaplasia and Smoking: An Integrative Review

By Lucas Gabriel Silva Ferreira, Rita de Cássia Silva de Oliveira & Leila Maués Oliveira Hanna

Abstract- Necrotizing Sialometaplasia (NS) is a benign, self-limiting rare inflammatory condition that involves the salivary glands tissues and simulates a malignant process. The etiology of this lesion is still not fully understood. The aim of this study was observe and evaluate the profile of this condition and its association with smoking. This integrative review followed six methodological stages and evaluated only case reports published from 1973 to 2022. It was analyzed 134 cases which 25% of them were associated with smoking. Others clinical features were also observed and described. Although the NS is a rare condition, it is necessary to know and understand, so as not to confuse this lesion with a malignant neoplasm and apply inappropriate treatments that may impair the patient's quality of life.

Keywords: *salivary glands; diagnosis; tobacco; case reports.*

GJMR-K Classification: *NLM: WU 140*

Strictly as per the compliance and regulations of:

Association between Necrotizing Sialometaplasia and Smoking: An Integrative Review

Lucas Gabriel Silva Ferreira [α], Rita de Cássia Silva de Oliveira [σ] & Leila Maués Oliveira Hanna [ρ]

Abstract- **Necrotizing Sialometaplasia (NS) is a benign, self-limiting rare inflammatory condition that involves the salivary glands tissues and simulates a malignant process. The etiology of this lesion is still not fully understood. The aim of this study was observe and evaluate the profile of this condition and its association with smoking. This integrative review followed six methodological stages and evaluated only case reports published from 1973 to 2022. It was analyzed 134 cases which 25% of them were associated with smoking. Others clinical features were also observed and described. Although the NS is a rare condition, it is necessary to know and understand, so as not to confuse this lesion with a malignant neoplasm and apply inappropriate treatments that may impair the patient's quality of life.**

Keywords: salivary glands; diagnosis; tobacco; case reports.

I. Introduction

Necrotizing Sialometaplasia (NS) was first described in 1973 by Abrams, Melrose and Howell[1]. It is characterized as a rare inflammatory process that involves the salivary glands and that in many cases represents a challenge for diagnosis, since it simulates a malignant process[2,3].

In general, the lesion initially appears as a nodule that later evolves into a central ulcer and resolves spontaneously in an average period of 8 to 10 weeks[3-5]. In about 75% of cases, NS develops on the palate[5]. The cause is commonly linked to local ischemia that generates necrosis of the salivary glands, although the etiological process has not fully understood yet [4,6].

SN is a rare lesion, cited in only 0.03% of biopsies of oral lesions, although this value can be uncertain, since it is poorly recognized and often confused with other lesions[3,5]. NS occurs mostly in male patients, especially in the fourth decade of life[5]. In addition, local trauma, drug abuse and smoking are factors that may be related to the appearing of SN[4].

In this sense, it is understood that tobacco use continues to be a public health problem worldwide, since about 23% of adults in the world smoke tobacco and its derivatives[7]. The main pharmacologically active substance in tobacco smoke is nicotine, a sympathomimetic drug[8]. In addition, many other potentially harmful substances are released during tobacco combustion, including carbon monoxide (CO), a compound known for its ability to impede the transport of oxygen through the bloodstream[8,9].

Therefore, it is relevant to investigate and understand the etiology of NS, since this lesion is misdiagnosed both clinically and microscopically, often being confused with malignant neoplasms, generating inappropriate and aggressive treatments[2,5].

Thus, this study aimed to observe and evaluate the profile of NS over the years, gathering clinical information about this condition from cases published in the literature, emphasizing cases associated with smoking.

II. Material and Methods

This integrative literature review was developed from 6 methodological stages[10] (figure 1) and is configured as an exploratory, retrospective review of an analytical nature.

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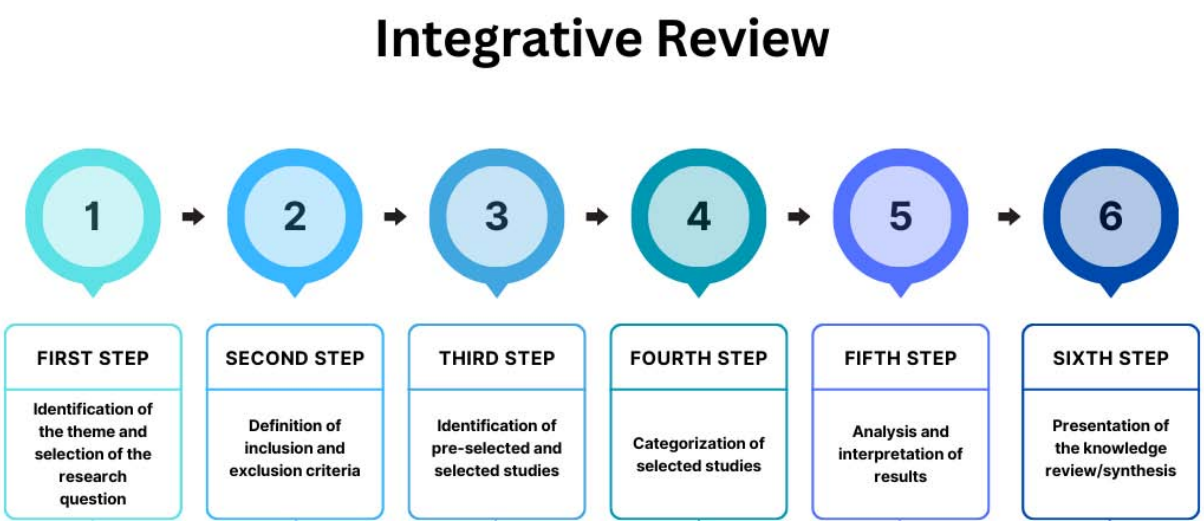

Fig. 1: Stages of the integrative review adapted from Botelho et al. (2011)

The first stage consisted of preparing the guiding question, which determined which studies would be included, the means adopted for identification and the information collected from each of the selected studies. The guiding question used was "what is the relationship between smoking and necrotizing sialometaplasia?".

The second stage consisted of a broad and diversified search in electronic databases. In this sense, the database used was from the National Library of Medicine, USA in its PubMed interface (www.pubmed.com.br), Latin American and Caribbean Literature in Health Sciences (LILACS) (lilacs.bvsalud.org), and Science Direct (sciencedirect.com), using the MeSH term "Necroziting Sialometaplasia".

The results were filtered in order to obtain only case reports published since the first time the disease was described (1973) until 2022; there were no time limits or language limits. All citations were entered into the Mendeley Reference Manager.

The third stage served to extract data from the selected articles, for which a table was built showing information about each article, namely: article title, research objective, target population and main idea of the article.

In the fourth stage, a critical analysis of the included articles was carried out, based on their complete reading. Then, data extraction was performed, which took place through an online spreadsheet, where research information, clinical characteristics and additional information were compiled as shown in table 1.

Table 1: Data extraction

Research information	Author
	Publication date
	Country where the studies were published
Clinical features	Age
	Gender
	Location
	Clinical presentation
	Evolution
	Associated condtitions
Additional information	Histological interpretation
	Treatment and prognosis
	Additional observations

Source: Authors

The fifth phase was developed from the discussion of the results, considering the interpretation and analysis of the articles, comparing the data evidenced in the analysis of the articles to the theoretical framework. At that moment, emphasis was placed on observing how many patients had smoking as an associated condition, in addition to identifying possible gaps in knowledge.

In the sixth and last phase, the final part of the research was developed, which is characterized by the analysis of the data and the preparation of the article, as well as the visual resources contained therein.

III. Results

From the data search carried out, following the strategy mentioned above, 352 studies were found. However, after reading the abstracts, only 80 studies[1-6,11-84] were selected to be read in full, since the other studies had research bias and/or were duplicated.

The included studies were published from 1973, when NS was first described, until the year 2022. During this period, the years with the highest number of published studies were 2004, 2009, 2016 and 2020. Most recurrent place of publication was the United States (21), followed by Brazil (8), Japan (6), among others (figure 2).

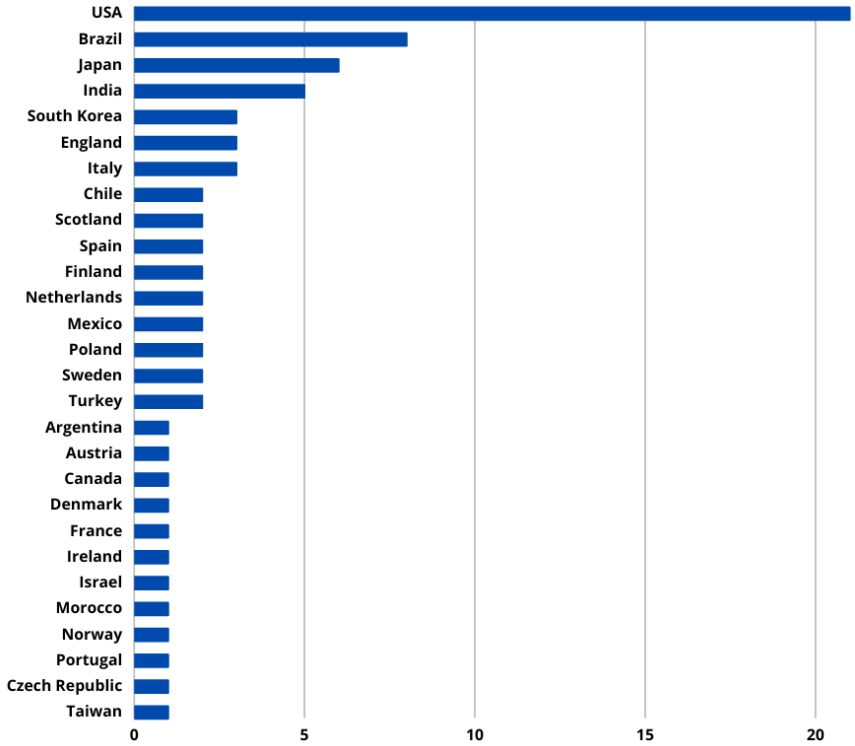

Fig. 2: Country where the studies were published

From the 80 included studies, it was possible to extract 134 cases. From this total, 78 cases (58.2%) were male patients and only 56 (41.8%) were female patients, which suggests a higher prevalence of the condition in men. Another relevant data was the general average age of the individuals, which was 43 years old, with the average age for men being 46 years old and for women being 38 years old.

Analyzing the clinical aspect of each case presented in the articles, it was possible to notice that the lesion is predominantly in the form of an ulcer (91 cases) and is also recurrent in the form of a swelling (29 cases), as illustrated in figure 3.

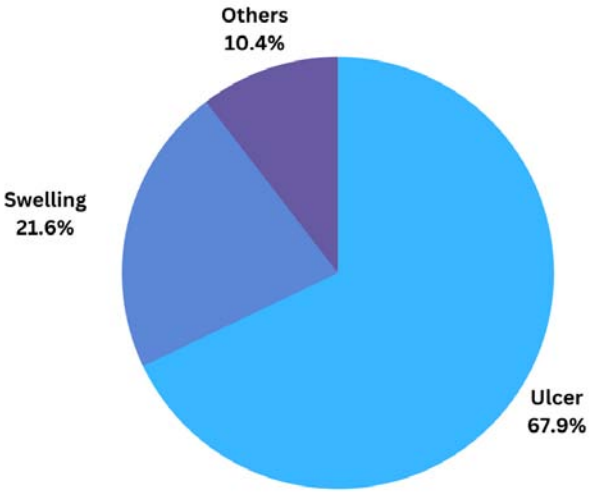

Fig. 3: Clinical presentation of the lesion in the cases studied

The most recurrent location of the lesion was on the hard palate (59% of cases), mostly unilateral, especially on the left side (figure 4A). Other regions, such as the junction of the hard and soft palate, the parotid glands, and others, were also affected by NS, as shown in figure 4B.

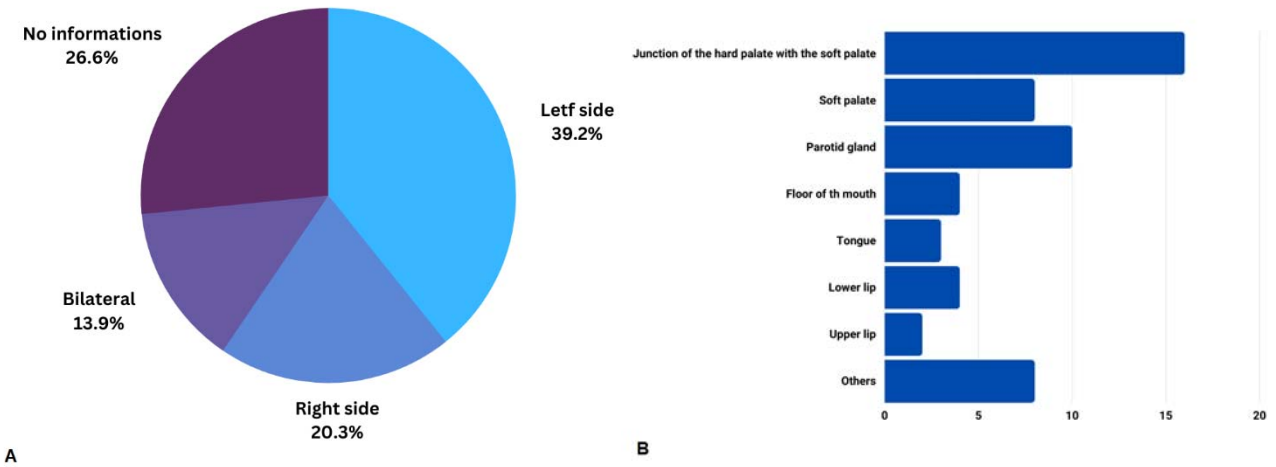

Fig. 4: A) Distribution of the occurrence of lesions on the hard palate in the cases studied; B) Other locations of the lesion in the cases studied.

The condition associated with the appearance of the most recurrent lesion, presented in the articles, was smoking (25%), isolated or associated with some other condition, mainly alcoholism (figure 5A). Furthermore, other adjacent conditions were also reported in the studies, such as oral malignant neoplasms, especially adenoid cystic carcinoma, in addition to trauma, use of prostheses and others (Figure 5B).

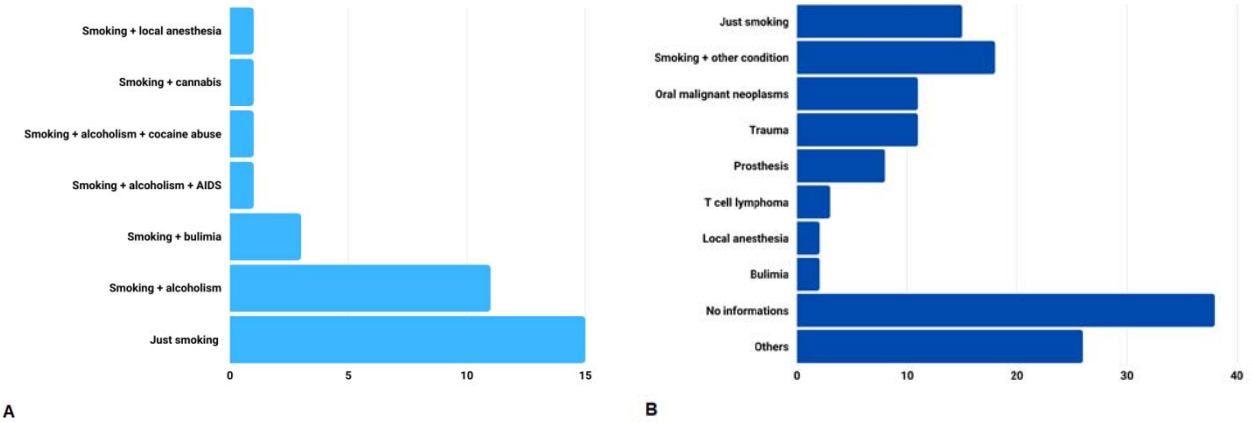

Fig. 5: A) Cases associated with smoking; B) Cases associated with other conditions.

The vast majority of cases were correctly diagnosed through biopsy. In only 10 cases there was confusion in the interpretation of the diagnosis. In 8 of them, the lesion was misdiagnosed as squamous cell carcinoma; in 1 case, as mucoepidermoid carcinoma and another one, as both. Surgical treatment was performed in 7 of the 10 inadequately diagnosed cases.

About 65% of the cases own resolved spontaneously, without the need for intervention. There was surgical treatment in 21% of cases and pharmacological intervention in 3% of cases, as shown in figure 6.

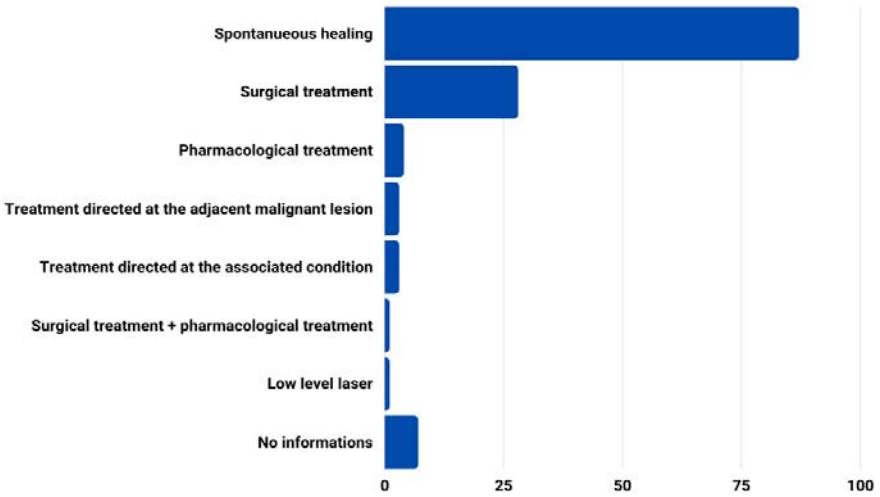

Fig. 6: Resolution of clinical cases.

Therefore, it was possible to notice that 1 out of 4 cases of NS were associated with smoking. Furthermore, of this total (33 cases), 31 cases (94%) presented as ulcerated lesions. In addition, as in the general analysis, the most recurrent location of the lesion was the hard palate (70%), but other regions such as the junction of the hard palate with the soft palate and the lower lip were also recurrent.

The average age of smokers was 43 years old, which is the same mean of the total number of patients analyzed. The patients were also mostly men (63%). Additionally, 22 cases resolved spontaneously, while 10 underwent surgical treatment and the rest were not reported. Finally, 5 cases were misdiagnosed at some point before the correct diagnosis was closed and all of them were treated surgically.

IV. Discussion

NS is an uncommon, benign, self-limiting, necrotizing inflammatory lesion that affects salivary gland tissues[6]. It presents an etiology that is still not fully understood, although it is already accepted that the development of the lesion occurs from a local ischemia, as previously discussed. This local ischemia generates, consequently, an infarction that generates tissue necrosis, followed by repair and metaplasia[11].

Several associated conditions are suggested as risk factors for the development of NS, including local trauma, local anesthesia, intubation trauma, chemical irritation caused by recurrent vomiting, as in cases of bulimia, in addition to tobacco use[12].

It is suggested by authors that physical, chemical or biological injuries to blood vessels are capable of producing ischemic changes, causing local infarction and the development of SN[13]. In this sense, the literature understands that tobacco use can cause local ischemia due to the vasoconstrictor effect of the substance[14].

Histologically, NS is characterized by acinar necrosis at the beginning of the lesion, followed by an association of squamous metaplasia of the salivary ducts. In this context, although necrosis occurs, the lobular architecture of the affected glands is still preserved. Briefly, the histopathological criteria for diagnosing this condition are coagulative necrosis of the acini in initial lesions and squamous metaplasia and reactive fibrosis in more advanced lesions; Besides histologically benign nuclear morphology; pseudoepitheliomatous hyperplasia of the lining epithelium; mucus release; intact lobular architecture[15].

The results of this study demonstrate a predominance of the lesion in men, as already recognized in the literature[16]. In addition, the occurrence of this condition was mainly concentrated between the 4th and 6th decade of life. However, it was possible to observe rare cases which NS manifested itself in young patients, aged less than 20 years, the most atypical case being that of a 2-year-old child[17].

The importance of understanding this lesion is related to the fact that it is remarkably similar to a malignant process, clinically and histologically[18]. Because of this, inadequate diagnoses can happen, leading professionals to opt for inappropriate or unnecessary treatments[19].

NS was misdiagnosed as a malignant lesion in some cases analyzed by this study, and surgical intervention was required in almost all of them. Thus, it is possible to see how a wrong diagnosis leads to an inadequate approach capable of further impairing the quality of life of a patient who is already conditioned to NS symptoms.

NS is an injury capable of causing a lot of pain to the affected patient[20]. According to the analyzed cases, the most predominant clinical presentation was in the form of an ulcer, although many cases without the presence of ulceration were also associated with pain. In addition, in many cases, the lesion started as a swelling and later evolved into an ulcer.

Furthermore, the most recurrent location of the lesion among the analyzed cases was the hard palate and, in many cases, the patient reported difficulties in eating due to the pain and sensitivity of the affected area. On the other hand, there were also reports of lesions in other regions, including those outside the oral cavity, such as the maxillary sinus[21].

Another case that draws attention is the one reported by Jeong et al. (2015)[22], which there was a recurrence of the lesion after 5 months of healing of the first lesion, something even rarer to happen and rarely reported. In the first clinical condition presented by the 36-year-old patient, a smoker, NS occurred in the form of an ulcer on the left side of the hard palate. After 5 months, when the symptoms reappeared, the lesion showed the same clinical presentation, but on the opposite side of the hard palate.

Among smokers, the most frequent region was the hard palate, as well as in cases in general. However, smokers had other regions affected by NS such as lower lip, mouth floor, parotid gland, and buccal mucosa.

The associated condition most observed among the patients in the cases studied was smoking, as already mentioned, demonstrating a possible association between this substance and the NS etiology. However, the etiology remains misunderstood and the fact that the lesion is rare, few records are made in the literature. In addition to the rarity of the lesion, there are also cases in which the lesion is confused, mainly by squamous cell carcinoma and mucoepidermoid carcinoma, which may also be a factor that hinders the dissemination of more cases in the literature.

V. Conclusion

Necrotizing Sialometaplasia is an injury that, although rare, is important to be recognized in order to avoid diagnostic confusion, as well as inappropriate treatments that may harm the quality of life of the patient affected by this condition. Although the etiology is still unclear, the results of the present study demonstrated a truly relevant quantitative relationship between the occurrence of the lesion and smoking, suggesting this condition as one of the main risk factors for the appearance of Necrotizing Sialometaplasia.

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Sing in the Pandemic for Health – The Science of it

By Prof. Maria Kuman, PhD
Holistic Research Institute

Abstract- The article explains how the emotional uplift during singing and the sounds themselves influence positively our health. If so, sing for health during the Pandemic.

Keywords: singing; emotional impact of singing; health effect of singing; singing and the emotional spirit.

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I. We are Emotional

We are emotional creatures. Proof of this is the fact that we cannot live only with the food that feeds the material body, we crave Love, which is the food for our emotional Spirit [1]. This means that we are a material body and emotional Spirit. Strangely, our science and medicine claim that we are only material body. They refused to consider the important role emotions play in our life, health, and wellbeing [1]. However, the Heart Math Institute in California (a free-lance institution) found that meditating on Love makes the functioning of the heart, lungs, and brain more harmonic [2], and harmonic functioning organs means healthy organs. This means that meditation on Love and the emotion of Love make us healthier.

II. The Denial that we are Emotional

If our science denies the existence of the emotional Spirit (and the important role emotions play in our life and health), it is because the Spirit is a very weak field (1,000 times weaker than the field created by the biocurrents of the material body). If so, it is difficult but not impossible to measure this weak field. I studied this weak field for more than 30 years and I developed sensitive equipment that allowed me to measure it [3]. I started my studies with photographing the aura with Kirlian photography, which uses high frequency electric field to multiply the photons of the weak aura and make it photographable. I found that when we experience positive emotions the aura is brighter, but when we experience negative emotions the aura is dimmer, i. e. I found that the aura is emotionally sensitive.

III. The Aura is Emotional and it is our Emotional Spirit

Since we say we are in high Spirit when we experience positive emotions and we say we are in low Spirit when we experience negative emotions, I concluded that the emotional aura must be our emotional Spirit. Then I found that the ancient Jewish Cabala was teaching to high priest that the aura was our Spirit. I found with measurements with my sensitive equipment that the weak field of the emotional aura (Spirit) ruled and regulated everything in the body, and is the one that made possible the functioning of our organs to be modulated by emotions. I also found that the weak field of the emotional aura (Spirit) ruled and regulated everything in the body not with its strength, but with the information this field carried. Since only nonlinear fields can imprint information, I decided that the field of the aura (Spirit) must be nonlinear electromagnetic field (NEMF) [3].

IV. The Vortices and Anti-vortices of the Emotional Aura (spirit) NEMF Called Chakras

Nonlinear fields have alternating vortices spinning clockwise and anti-vortices spinning counterclockwise. With my supersensitive equipment, I was able to measure the alternating vortices and anti-vortices of the aura (Spirit) NEMF, which are along the backbone numbered from bottom to top (Fig. 1) [3]. They are called "chakras" in Hindu texts, which means "spinning wheels" in Sanskrit. The first 6 chakras rule the 6 glands of internal secretion, which by releasing hormones in the blood in amount mg/litter rule and regulate everything in the body. The seventh chakra on the top of the head rules, regulates, and integrates the function of all 6 grands [4].

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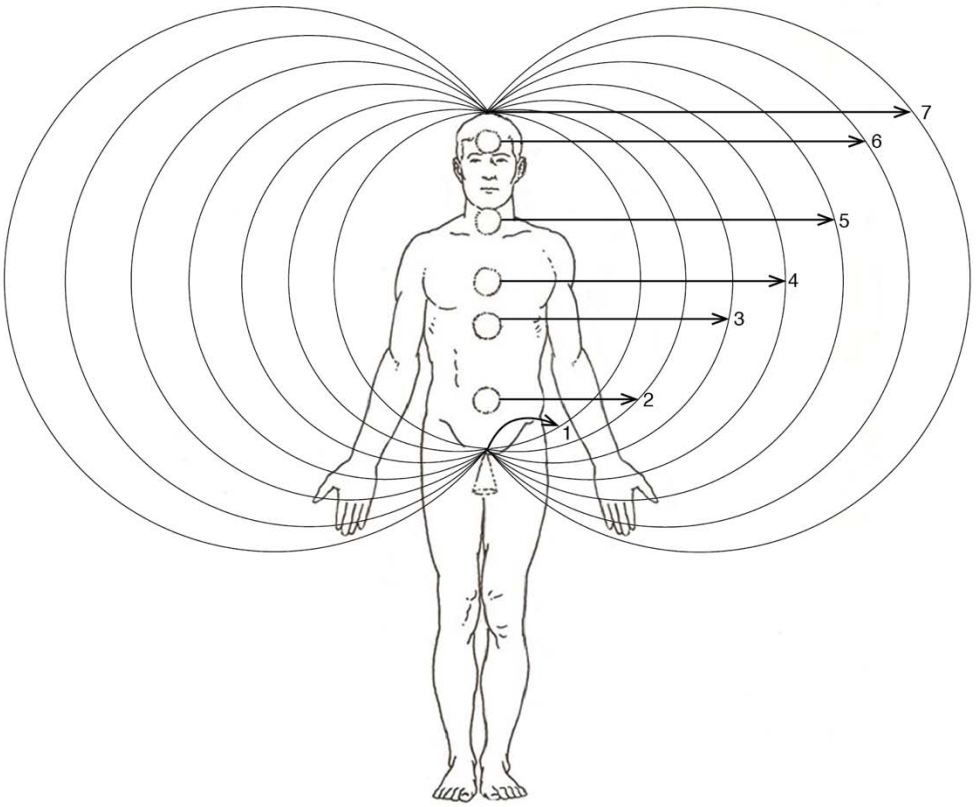

Fig. 1: The seven chakras along the backbone and their corresponding seven discrete energy levels

1/ The first chakra (called Base Chakra) has frequency 4 Hz and consists of 4 sub-spirals with common origin – they are like 4 curled snakes with heads together. (The anatomy of the vortices was first observed in vitro by Krinski and it was cited in the book of Prigogine [4]). The fist chakra rules the function of the adrenal glands and relates to our survival instincts. It is red in color and is activated by red color. It responds and is activated by the sound oo. It governs the spinal column and the kidneys [5].

2/ The second chakra (called Sacral Chakra) has frequency 6 Hz and consists of 6 sub-spirals with common origin. It rules the function of the gonads and relates to our sexual desires. It is orange in color and is activated by orange color. It responds and is activated by sound oh. It governs the reproduction, the lymphatic system, and the lower abdomen[5].

3/ The third chakra (called Solar Plexus) has frequency 10 Hz and consists of 10 sub-spirals with common origin. It rules the function of the digestive system. It is yellow in color and is activated by yellow color. It responds and is activated by sound aw. It governs Stomach, Liver, Gall Bladder, Pancreas, and the whole metabolic energy [5].

4/ The fourth chakra (called Heart Chakra) has frequency 12 Hz and consists of 12 sub-spirals with common origin. It rules the function of the heart and is considered the seat of our emotional Soul. It is green in color and is activated by green color. It responds and is activated by sound a. It governs the Heart, Lungs, blood and blood vessels, and the Vagus nerve [5].

5/The fifth chakra (called Throat Chakra or Chakra of Communication) has frequency 16 Hz and consists of 16 sub-spirals with common origin. It rules the function of the Thyroid gland and relates to our ability to communicate. It is blue in color and is activated by blue color. It responds and is activated by sound e. It governs the verbal communication and singing [5].

6/ The sixth chakra (called Chakra of Intuition) has frequency 96 Hz and consists of 96 sub-spirals with common origin. It rules the function of the Pineal Gland and relates to our intuitive vision, creativity, and clairvoyance – ability to foresee the future and see the past. It is indigo in color and is activated by indigo color. It responds and is activated by sound om. It governs the intuition, the creativity, and the ability to see with the mind the past and the future of the people and the Universe [5].

7/ The seventh chakra (called Crown Chakra) has frequency 972 Hz and consists of 972 sub-spirals with common origin. It rules and regulates the function of the whole body. It is white in color and is activated by white color. It responds and is activated by sound ee. It governs the thoughts, and determines the knowledge and the intellectual level of the individual [5].

While the first four chakras #1, #2, #3, and #4 are the chakras of the material body, chakras #6, #5, #4, and #3 are the chakras of the Spirit. If so, chakras #3 (Solar Plexus) and Chakra #4 (Heart Chakra) belong to both – the material body and the emotional Spirit. They are called chakras of the Soul because: a/ the Heart, which is emotionally-sensitive (chakra #4), is considered the seat of the Soul, and b/ the emotionally-sensitive digestion (chakra #3 Solar Plexus) is another seat of the Soul. This defines Soul as a unity of body and emotional Spirit.

Thus, the ancient knowledge on chakras, confirmed by my measurements of the chakras, claims that the chakras are sensitive to colors and sounds. If so, we can expect both colors and sounds to influence our emotional aura (Spirit), which rules and regulates everything in the body. If this is so, we can expect sounds from singing and from listening harmonic music to influence our emotional aura (Spirit), which rules and regulates everything in the body. However, we can expect the sound produced by the body during singing to have stronger effect on the body and Soul, than just listening to the sounds of music produced by somebody else. We can expect singing to emotionally uplift our Souls, and since Soul is the unity of material body and emotional Spirit, which rules and regulates everything in the body, we can expect singing to positively influence our health.

V. Conclusion

Thus, singing positively influences our emotional Soul, which is the unity of our material body and emotional Spirit. Since the emotional Spirit rules and regulates everything in the body and makes the functioning of our body to be modulated by emotions, singing by influencing positively our emotional Spirit is expected to influence positively the functioning of our body, i.e. to influence positively our health. If so, sing for health during the Pandemic.

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Accessing the Subconscious Quantum Computer Working with the Waves of Our Aura (Spirit) NEMF for Health

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Abstract- The article reveals the existence of a Quantum Computer in our Subconscious, of which we are not consciously aware. First hypnosis, which put the Conscious to sleep to access the Subconscious, revealed that hypnotized people with sleeping Conscious calculated at least 10,000 times faster. This meant that in the Subconscious we have a computer more powerful than our conscious computer. Farther studies revealed that the subconscious computer has unlimited possibilities to memorize and can predict events by jumps in the future or see past evens by jumps in the past. Since only Quantum Computers allow quantum jumps to the future or the past, it became obvious that in the Subconscious operates a powerful Quantum Supercomputer. Since Quantum Computers operate with waves, the waves of our aura (Spirit) field must be involved, which I found to be nonlinear electromagnetic field (NEMF).

Keywords: quantum computer (QC); accessing the quantum computer; enlightenment is QC access; intuitive creativity is QC access; clairvoyant abilities are QC access; telepathic abilities are QC access.

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Keywords: quantum computer (QC); accessing the quantum computer; enlightenment is QC access; intuitive creativity is QC access; clairvoyant abilities are QC access; telepathic abilities are QC access.

I. Introduction

I was the first to speak that we must have a Quantum Computer in our Subconscious, of which we are not consciously aware [1]. First, the fact that hypnosis revealed that hypnotized individuals with sleeping Conscious did calculations very fast, meant that a powerful supercomputer must operate in the Subconscious. Second, the fact that some people can foresee the future and see the past and only Quantum Computers could make quantum jumps to the future and the past, meant that the powerful supercomputer in the Subconscious must be a Quantum Computer operating with waves [2].

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II. The Quantum Computer must Work with the Waves of our Aura NEMF

Hypnosis also revealed that the powerful Quantum Computer had a huge storage capacity – it stored not only the memories of this lifetime with details; it also stored the memories of previous lifetimes [9]. Records are very compact only when they are done with waves - visual images, hearing, smelling, and tactile memories could be stored as compact three-dimensional holographic records [7]. Since holographic images are created only with laser light, it seems that our Quantum Computer operates in the Subconscious with the waves of our aura ("aura" means "light"), which I found to be nonlinear electromagnetic field (NEMF).

I measured the weak nonlinear electromagnetic field (NEMF) of the aura for 40 years. I found that our aura NEMF is emotional and is 1,000 times weaker than the field created by the biocurrents of our material body. I also found that this weak field rules and regulates everything in the body not with its strength, but with the information it carries (nonlinear fields do not dissipate and can imprint information). I had to develop and patent very sensitive equipment to be able to measure it [3], [4], [5]. My measurements revealed that the weak aura NEMF is emotional: at positive emotions it is brighter, at negative emotions - dimmer. Since we say we are in high Spirit when experiencing positive emotions and we say we are in low Spirit when experiencing negative emotions, I concluded that the aura must be our Spirit.

Therefore, the powerful Quantum Computer in the Subconscious works with the waves of the aura (Spirit). This powerful Quantum Computer is the source of: our intuitive creativity [6], our ability to see with our mind holographically [7], our clairvoyance (ability to foresee the future or see the past [8]), and our telepathic abilities, which are communications with nonlinear waves between the Quantum Computers of the two telepathically connected individuals. The Quantum Computer can also diagnose and heal. It should not be surprising that the Creator wisely restricted the access to the powerful Quantum Computer - only highly Spiritual individuals, who meet some moral criteria, were allowed to have access to it.

III. Levels of Spirituality and the Access to the Powerful Quantum Computer

As explained in my article [10], our material body has 7 energy levels and our Spirit has 7 possible energy levels, of which only 5 spiritual levels could be achieved on Earth, i.e. 8th, 9th, 10th, 11th, and 12th (details on this can also be found in my books [11] and [12]). However, about 90% of the Spirits living on Earth are Young Spirits (energy level 7). They are happy to be in a material body and enjoy the good food and good sex, which the material world offers. They are without any Spiritual interests and do not have any Spiritual awareness.

1/ According to Valerie Hunt [13], the major frequency of the aura of the people without spiritual interests is 200 Hz. These are the majority of people (~90%). They are Young Spirits, who deny the existence of the Spirit (they claim we are only a material body) and if so don't expect them to acknowledge the presence of Quantum Computer in the Subconscious operating with the waves of the Spirit.

2/ According to Valerie Hunt [10], [13], the people showing some telepathic and clairvoyant abilities, which mean they have access to the Quantum Supercomputer, have auras (Spirits) with a major frequency from 400 Hz to 800 Hz. These are the individuals with 9th, 10th and higher Spiritual levels, who have intuitive insights (known under the name "deja vou"), which means they have access to the Quantum Computer. Obviously, the Creator, who is Supreme Intelligence, wisely allowed only individuals with High Spiritual Levels (who meet some moral criteria) to have access to the powerful Quantum Supercomputer, which operates with the waves of the Spirit. The ways to spiritually grow and achieve Higher Spiritual Levels (with high major frequencies) are revealed in my book [11].

When the 12th Spiritual Level is reached (the highest possible on earth), the person has learned how to handle the emotions of the Spirit and to suppress the ego of the material body, which comes from the survival instincts of the body. Then the Spirit can leave the Earth and don't need to come back any more unless it volunteers to come (usually in times of transition) [9]. The Spirits with levels 12th (and higher) that volunteered to come to Earth are called Transcendental Spirits and Jesus was such Transcendental Spirit. He volunteered to come to the Earth (to live in a material body) to teach us how to spiritually grow - by loving, forgiving, and helping others.

The different Spiritual levels can be seen on Kirlian photographies because the aura (Spirit) has different shape at different Spiritual levels. The Kirlian photography is done in high frequency electric field, which multiples the photons of the weak aura, and makes it photographable. Fig. 1 is a Kirlian photography of author's aura in 1991 - it illustrates Spiritual level 9. The light ball is "the crawn", which illustrates that the person is in "the Kingdom of God" (these are the people that have access to the powerful Quantum Computer). The auras of the people with Spiritual levels 10, 11, and 12 have a light ball on top of the head, which is: 2 feet from the top of the head for Spiritual level 10th, 3 feet from the top of the head for Spiritual level 11th, etc.

Fig. 1: Kirlian photo of author's aura in 1991 – Spiritual level 9

IV. Accessing the Quantum Computer during Meditation or Prayer

Russian scientists found with EEG measurements that during meditation and prayer the conscious mind is sleeping (EEG does not register on the surface of the brain any activity only the basic alpha-rhythm), just like during hypnosis. This means that all three: meditation, prayer, and hypnosis put the Conscious to sleep to allow access to the Subconscious and its powerful Quantum Supercomputer, which works with the waves of our aura (Spirit) NEMF.

In my article [14]: "Science for the Effect of Prayer", it was revealed that Russian scientists also found that prayer increases the vibrational frequencies of the NEMF of our Spirit, which means that the more we pray, the more spiritual we become. It takes a lot of prayer, meditation, and righteous living (loving, forgiving, and helping others) to grow spiritually enough to be accepted in the Kingdom of God and get access to the Quantum Computer.

V. Accessing the Quantum Computer during or after Sleep

Our sleep is constant alternative switches between light sleep and deep sleep. During light sleep, judging by the EEG activity registered on the surface of the brain, the Conscious is active, and this is when we dream. During deep sleep, only galvanic response is registered from deep areas of the brain, which is specific for emotional response, which means that during deep sleep the emotional Spirit located in the Subconscious is active. During these switches, the information recorded during the day in the Conscious is read and sent for permanent storage in the Quantum Computer in the Subconscious as a compact holographic (tri-dimensional) record done with the waves of our aura (Spirit) NEMF [6].

During these alternative switches Conscious <-> Subconscious, information can also be transferred from the Subconscious to the Conscious and appear in our dreams. We call these dreams prophetic because coming from the Quantum Computer of the Subconscious they could be leaps to the future. Having prophetic dreams is quite specific for individuals with spiritual levels 9, 10, and 11, while for spiritual level 12 the revelations usually come after sleep or during meditation or prayer. Jesus was going to secluded places to meditate or pray, so that God can reveal to him (through the Spirit in the Subconscious) what is the right thing to say or do.

Many people think that Jesus was going to secluded places to contemplate. Meditation is opposite to contemplation. While contemplation is active thinking manifested with strong EEG activity of the Conscious brain, meditation is zero activity of the Conscious brain, which allows access to the Quantum Computer in the Subconscious working with the waves of the Spirit. Obviously, to make us creative like him, the Creator (God) made us emotional (like him), but put our emotional Spirit in the Subconscious to give us freedom of choice – the biggest gift of the Creator to us [6]. Our emotional and creative Spirits' NEMF are holographic templates of the emotional and creative Hologram of the Creator [7].

VI. Enlightening is Access to the Quantum Computer

Sakyamuni Buddha ("Buddha" means "awaken") wanted to become enlightened. (I intend to explain in this section what enlightenment means). He studied with two Tao Masters the art of meditation, which would allow him to stop the chattering of his Conscious mind, put it to sleep, and access the Subconscious. Buddha did succeed to get access to his Subconscious and became enlightened through accessing the treasure-box in it - the Quantum Computer. This allowed him to see with his Mind [6] how many thousands are the inhabited planets in the Milky Way [15].

2,600 years later, our modern science is still very far from knowing how many are the inhabited planets in the Milky Way. What our science does know is that our brain has two hemispheres: a logical left hemisphere, which is mostly related to the Conscious, and emotional right hemisphere, which is mostly related to the Subconscious. The two hemispheres are connected with Corpus Calosum – a cable of nerve fibers with the thickness of a finger, which connects both hemispheres. On top of Corpus Callosum is the Pineal Gland with size and shape of a pinecone [16], [17].

What our traditional science refuse to acknowledge is the role of emotions in our life and there is no creativity and enlightenment without emotions. Only when enough neurotransmitters of emotional excitation (glutamates) are released, the Pineal Gland becomes excited – it lightens up and bridges both brain hemispheres. Then the Digital Computer of the logical Conscious and the Quantum Computer of the emotional Subconscious are bridged to work as one whole piece [6].

Enlightenment or full intuitive creativity is a state, in which the digital Computer of the Conscious and the Quantum Computer of the Subconscious (which works with the waves of our emotional aura (Spirit)) work as one whole piece at the same level of over-excitement [6]. When this takes place, the person is fully connected to the Creator through the Quantum Computer working with the waves of his Spirit (which is template of the hologram of the Creator God) and is receiving information from the cosmic knowledge bank of the Creator God.

I think the so-called Celtic cross symbolizes spiritual enlightenment. The vertical line of the cross symbolizes the gap between the two brain hemispheres and the horizontal line – Corpus Callosum. The circle around the intersection of both lines symbolizes the shinning of the excited Pineal Gland on top of Corpus Callosum when flooded with neurotransmitters of emotional excitation. This bridges the Digital Computer of the Conscious and the Quantum Computer of the Subconscious (working with the waves of the emotional Spirit) and makes possible their synchronized work, which we call spiritual enlightenment [6].

Thus, spiritual enlightenment is receiving information from the cosmic knowledge bank of the Creator through the Quantum Computer in the Subconscious, which works with the waves of our emotional Spirit (a template of the hologram of the Creator). Such enlightenment can allow the person to see with his Mind what causes the health troubles (to intuitively diagnose) and to heal. Doctor Vitulcas from Greece is such gifted individual. As a patient entered his office he saw that she was having heart troubles and he even saw what caused the troubled – the husband. When he told her this her jaw dropped down… and he saw how to fix the problem.

VII. Conclusion

The article revealed the existence of a Quantum Computer in our Subconscious brain, which works with the waves of our emotional aura (Spirit) NEMF. To give us freedom of choice the Creator put the Spirit (and the Quantum Computer working with the waves of the Spirit) in the Subconscious. However, this made us not consciously aware of the existence of the Spirit and the Quantum Computer working with the waves of the Spirit.

The article explained that the Quantum Computer in the Subconscious is Super-Computer with a very high speed of computation and huge memory storage - it is the biggest gift of the Creator to us, which make us intuitive and creative. However, the Creator wisely restricted the access to the powerful Quantum Computer allowing only highly Spiritual people, who meet some moral criteria, to have access to it.

The article explained that only individuals with high Spiritual level, i.e. high frequency of their emotional aura (Spirit), have access to the Quantum Computer, which allows them to be clairvoyant, prophetic, heal the sick, and revive the dead, as Jesus did. We are now trying to build Quantum Computers and if we are wise, we should do the same as our Creator did – restrict the access to the powerful Quantum Computers.

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Introduction

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

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

FMRC

Fellow of Medical Research Council

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

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

To the institution

Get letter of appreciation

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

Exclusive Network

Get access to a closed network

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

Career | Credibility | Exclusive | Reputation

Certificate

Certificate, LoR and Laser-Momento

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

Career | Credibility | Exclusive | Reputation

Designation

Get honored title of membership

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

Career | Credibility | Exclusive | Reputation

Recognition on the Platform

Better visibility and citation

All the Fellow members of FMRC get a badge of "Leading Member of Global Journals" on the Research Community that distinguishes them from others. Additionally, the profile is also partially maintained by our team for better visibility and citation. All fellows get a dedicated page on the website with their biography.

Career | Credibility | Reputation

Future Work

Get discounts on the future publications

Fellows receive discounts on the future publications with Global Journals up to 60%. Through our recommendation programs, members also receive discounts on publications made with OARS affiliated organizations.

Career | Financial

GJ Internal Account

Unlimited forward of Emails

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

Career | Credibility | Reputation

Premium Tools

Access to all the premium tools

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

Financial

Conferences & Events

Organize seminar/conference

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

Career | Credibility | Financial

Early Invitations

Early invitations to all the symposiums, seminars, conferences

All fellows receive the early invitations to all the symposiums, seminars, conferences and webinars hosted by Global Journals in their subject.

Exclusive

Publishing Articles & Books

Earn 60% of sales proceeds

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

Exclusive | Financial

Reviewers

Get a remuneration of 15% of author fees

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

Financial

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Become a member of the Editorial Board

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

Career | Credibility | Exclusive | Reputation

And Much More

Get access to scientific museums and observatories across the globe

All members get access to 5 selected scientific museums and observatories across the globe. All researches published with Global Journals will be kept under deep archival facilities across regions for future protections and disaster recovery. They get 10 GB free secure cloud access for storing research files.

ASSOCIATE OF MEDICAL RESEARCH COUNCIL

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

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Earn 60% of sales proceeds

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

Exclusive | Financial

Reviewers

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Financial

And Much More

Get access to scientific museums and observatories across the globe

All members get access to 2 selected scientific museums and observatories across the globe. All researches published with Global Journals will be kept under deep archival facilities across regions for future protections and disaster recovery. They get 5 GB free secure cloud access for storing research files.

Associate	Fellow	Research Group	Basic
$4800 **lifetime designation**	$6800 **lifetime designation**	$12500.00 **organizational**	APC **per article**
Certificate, LoR and Momento **2** discounted publishing/year **Gradation** of Research **10** research contacts/day **1 GB** Cloud Storage **GJ** Community Access	**Certificate,** LoR and Momento **Unlimited** discounted publishing/year **Gradation** of Research **Unlimited** research contacts/day **5 GB** Cloud Storage **Online Presense** Assistance **GJ** Community Access	**Certificates,** LoRs and Momentos **Unlimited** free publishing/year **Gradation** of Research **Unlimited** research contacts/day **Unlimited** Cloud Storage **Online Presense** Assistance **GJ** Community Access	**GJ** Community Access

Preferred Author Guidelines

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

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

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

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

Before and during Submission

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

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

Declaration of Conflicts of Interest

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

Policy on Plagiarism

Plagiarism is not acceptable in Global Journals submissions at all.

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

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

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

- Printed material
- Graphic representations
- Computer programs
- Electronic material
- Any other original work

Authorship Policies

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

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

Changes in Authorship

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

Copyright

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

Appealing Decisions

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

Acknowledgments

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

Declaration of funding sources

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

Preparing your Manuscript

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

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

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

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

A research paper must include:

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

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

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

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

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.

Format Structure

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

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

Author details

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

Abstract

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

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

Keywords

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

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

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

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

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

Numerical Methods

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

Abbreviations

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

Formulas and equations

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

Tables, Figures, and Figure Legends

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

Figures

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

Preparation of Eletronic Figures for Publication

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

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

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

Tips for writing a good quality Medical Research Paper

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

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

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

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

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

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

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

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

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

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

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

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

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

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

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

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

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

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

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

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

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

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium 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.

Mistakes to avoid:

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

Title page:

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

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

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

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

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

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

Approach:

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

Introduction:

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

The following approach can create a valuable beginning:

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

Approach:

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

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

Procedures (methods and materials):

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

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

Materials:

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

Methods:

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

Approach:

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

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

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

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

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

Content:

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

What to stay away from:

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

Approach:

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

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

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

Figures and tables:

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

Discussion:

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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.

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	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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