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Impact of COVID-19 Pandemic on Mental Health of Health Care Workers. A Systematic Review in Low-and Middle-Income Countries

By Alisha Timsina, Sonia Kaundal & Kabita Parajuli

Abstract- *Background:* Coronavirus disease which is threatening the global world started in 2019. It has created a higher risk of infection and death to health workers due to excessive exposure to covid 19. This review aimed to find the mental health impacts of covid 19 among health care workers in low and middle-income countries.

Method: Online databases EBSCOhost, PubMed, and Google Scholar were used to identify published articles evaluating the effects of the covid 19 on the mental health of health workers. The search was restricted to studies conducted from 01/01/2020 to 29/02/2021in the English language. All cross-sectional studies and observational studies were considered if they focused on the effects of covid 19 on the mental health of health care workers. This review was based on Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) followed by the flowchart. The quality of cross-sectional studies was done using a Quality assessment checklist for prevalence studies.

Keywords: *covid 19. mental health, health care workers.*

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Impact of COVID-19 Pandemic on Mental Health of Health Care Workers. A Systematic Review in Low-and Middle-Income Countries

Alisha Timsina [α], Sonia Kaundal [σ] & Kabita Parajuli [ρ]

Abstract- ***Background:*** Coronavirus disease which is threatening the global world started in 2019. It has created a higher risk of infection and death to health workers due to excessive exposure to covid 19. This review aimed to find the mental health impacts of covid 19 among health care workers in low and middle-income countries.

Method: Online databases EBSCOhost, PubMed, and Google Scholar were used to identify published articles evaluating the effects of the covid 19 on the mental health of health workers. The search was restricted to studies conducted from 01/01/2020 to 29/02/2021in the English language. All cross-sectional studies and observational studies were considered if they focused on the effects of covid 19 on the mental health of health care workers. This review was based on Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) followed by the flowchart. The quality of cross-sectional studies was done using a Quality assessment checklist for prevalence studies.

Result: From 2525 records retrieved and screened, 9 full-text articles were included in the final review (8 cross-sectional, and 1 observational study). Findings illustrate that anxiety, depression, and stress were the most common mental health outcomes among health workers working during the covid 19 periods. Mental health problems are more prevalent among female health workers as compared to males, but no studies analyze that it might be because of the huge amount of female workforce than male.

Conclusion: The healthcare workforce either frontline or onsite is at higher risk of negative mental health consequences. There is a need for interventional studies to combat thesis problems and maintain a healthy workforce. Psychological counseling, meditation, reducing the length of shifts, and increasing the number of health workforce with proper personal protective equipment could reduce mental health problems.

Keywords: covid 19. mental health, health care workers.

I. Introduction

COVID pandemic first originated in Wuhan, China and has spread domestic and internationally. This virus was also given name as Severe Acute Respiratory Syndrome Coronavirus (SARS COV-2). World health organization had declared the Coronavirus pandemic as a public health emergency. This virus has affected millions of lives and still poses a serious public health threat globally. By 1 June 2020, after 6 months of the outbreak, the virus had spread to more than 198 countries with more than 6,040,609 confirmed cases and 370,657 deaths reported and was therefore considered a global pandemic. Corona-virus pandemic possessed an increasing demand for public health care workers (World Health Organization, 2020).

This pandemic had severely burdened and overwhelmed the health care systems including the health care workers (Armocida et al., 2020). The World Health Organization and governments across the world have laid stress on health care workers to prevent or minimize the risks and save the lives of the patients (WHO, 2020). Both the frontline and non-front line health care workers were at high risk of developing mental health consequences as they were directly involved in the treatment, care, diagnosis of the disease.

A study assessing 13 articles showed that Post-traumatic stress disorder, burnout, depression, and anxiety were the most common mental health problems associated with the health care workers' occupational activities during pandemics. Several reports indicated that the health care workers became infected with the COVID 19 pandemic when they were in close contact with the infected cases. As of reports, (Pappa et al., 2020) also revealed that as of March 2020, 29% of all hospitalized patients were health care workers. Health care workers are the vulnerable people for developing serious psychological consequences. Current studies showed that the growing number of suspected and confirmed cases, increasing death tolls, limited safety equipment and vaccines, overwhelming workload, feeling of inadequately supported, widespread media coverage etc. can lead to unwillingness to work, stress, anxiety which could have long term psychological implications on health care workers.

Likewise (Pappa et al., 2020) had evaluated thirteen research conducted on mental health of the health-care workers; they concluded that one in five health care workers experienced anxiety, depression and 2 out of 5 suffered from insomnia. Furthermore, (Vindegaard & Eriksen Benros, 2020) had assessed twenty studies which concluded that anxiety, depression, sleep problems were more prevalent in health care workers compared to the general population.

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II. Rationale

Till date, the literature on the mental health consequences regarding the impact of covid 19 on mental health care workers be easily found. However, there were no systematic reviews that have consistent results. Reviews that were done did not explain about what mental health problems are more common. The very few systematic reviews done before were not inclusive studies which focused on the impact on mental health of health workers working with people infected by COVID pandemic, and no review provided clear guidelines that might direct the leaders and practitioners on the planning of interventions. Furthermore, a consensus regarding the effects of COVID 19 pandemic on the psychological wellbeing of health care workers had not been reached yet.

To address this gap, systematic review was conducted to examine the evidence of the impact of COVID 19 outbreak pandemic on the psychological health of health care workers who worked in the hospital treating patients with covid. This study aimed to identify the evidence on the psychological impact of COVID 19 pandemic on the health care workers. Furthermore, the findings of the study could enable the leaders and practitioners to develop the interventions or recommendations to minimize the negative consequences in future.

III. Methods

This review was based on Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) followed by the flowchart. Hence it is systematic review ethical consent was not required.

IV. Eligibility Criteria

Inclusion criteria to consider studies followed the PICOS guidelines presented in Table 1.

Table 1: PICOS criteria for inclusion of studies

PICOS	Inclusion Criteria
Population	Health care workers
Exposure	Covid 19 pandemic
outcome	Mental Health Disorders
Setting	Lower middle-income countries Angola, Bangladesh, Kenya, Algeria, India, Honduras, Papua New Guinea, Philippines, Benin, Kiribati, Senegal, Bhutan, Kyrgyz Republic, Solomon Island, Bolivia, Lao PDR, Sri Lanka, Cabo Verde, Lesotho, Tanzania, Cambodia, Mauritania, Timor-Leste, Cameroon, Micronesia, Fed. Sts. Tunisia, Comoros, Moldova, Ukraine, Congo, Rep. Mongolia, Uzbekistan, Côte d'Ivoire, Morocco, Vanuatu, Djibouti, Myanmar, Vietnam, Egypt, Arab Rep. Nepal, West Bank and Gaza, El Salvador, Nicaragua, Zambia, Eswatini, Nigeria, Zimbabwe, Ghana, Pakistan, São Tomé and Principe.

V. Types of Studies

Cross sectional and observational studies were considered if the article were based on the physiological impact of covid 19 on health care workers. This study has excluded the duplicates of the same articles based on the same author and same countries. Studies conducted on the non-health care workers (General population) were excluded. Furthermore, articles that were irrelevant to the outcomes and only consisting of title and abstract were also excluded in this study.

VI. Data Source and Search Strategy

The online databases EBSCOhost, Google Scholar and PubMed were searched for literature. Searches were limited to studies that were published in English language from 2019 to 2021. The search strategy was based on PICOS criteria which is provided in Annex I.

VII. Study Selection

Articles selected according to the eligibility criteria were screened for inclusion in the review. After the selection, 901 duplicates were removed using Mendeley. Subsequently, titles and abstracts retrieved were assessed independently by two researchers (AT and KP) to identify articles that potentially met the eligibility criteria described previously. Any disagreement was discussed with the third researcher (SK) for final decisions. Afterwards, the full text of articles was

retrieved and assessed by two independent researchers (AT and KP) and any disagreement was discussed with a third researcher (SK) for validation.

VIII. Data Items and Extraction Process

Data from included studies were extracted independently by 2 researchers (MS and OO), using a Microsoft Excel spreadsheet. The spreadsheet included author, year of publication, journal or conference article, country, city, setting, study design, population details, sample size, age distribution, gender, measurement tools accessing mental health outcomes, and severity of outcomes. The results include mental health disorders due to covid 19 pandemic.

IX. Risk of Bias in Individual Studies

Individual studies were assessed independently by 2 researchers (AT and KP) and the disagreements were discussed with the third researcher (SK). Any uncertainty about the level of bias of an individual study was discussed until consensus was reached.

To evaluate the quality of cross-sectional studies the evaluation was done using Quality assessment checklist for prevalence studies. (Hoy et al. 2012). The tool allowed researchers to evaluate the target population of close representation of national population, sampling frame, sampling methods, non-response bias, reliability and validity, data collection methods, exposure method, incomplete outcome and overall risk of study (Hoy, et al, 2012). The quality assessment for all individual studies is summarized in Annex II.

X. Data-synthesis

Data were summarized narratively, and we have described exposure based on the information provided in the studies and also have tried to include data from figures, tables, charts from the included studies.

XI. Results

a) Study selection

Altogether 2525 records were retrieved through database searching. 901 articles were removed and remaining 1624 articles were screened to identify whether title and abstract were relevant or not. After screening, only 23 articles were left for full text screening. Out of 23 articles, 9 articles were selected that met the potential eligibility criteria of the study. The detail of study selection is shown in the flowchart in figure 1.

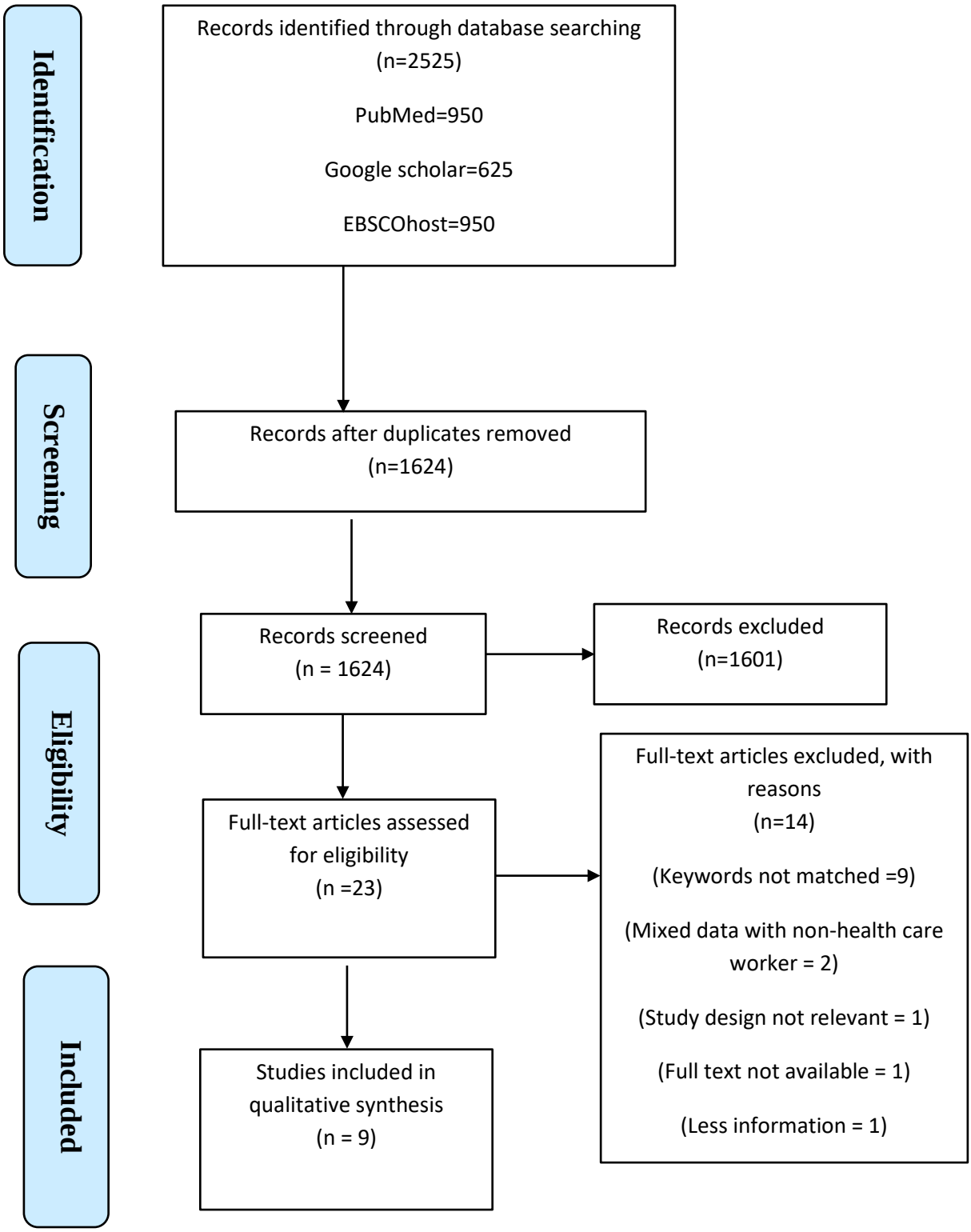

Figure 1: Prisma flowchart (PRISMA, 2009)

b) Study characteristics

Study characteristics of included studies are provided in Table 2. One study was conducted in Nepal (Khanal et al., 2020), one in Nigeria (Erinoso et al., 2020), two in Pakistan (Arshad et al., 2020, Sandeshet al., 2020), two in Bangladesh (Tasdik Hasan et al., 2020, Khatun et al., 2021) and one in Vietnam (Than et al., 2020), one in Malaysia (Chow et al., 2021), one in India (Raj et al., 2020).

Eight studies were cross-sectional, and one was observational study. Out of 9 studies retrieved, four studies were conducted online through web -based surveys, 2 studies were conducted through structural self-reported questionnaires and 3 through structural questionnaires. All the surveys were hospital-based. The age of participants ranged between 20-50years. This paper included the population from low- and middle-income countries. The sample size ranged from 105-475 participants across studies. All papers were published journal articles between 2020 to 2021.

c) Prevalence outcomes of mental health disorder due to Covid-19 pandemic

Study findings are provided in Table 3. All nine studies reported prevalence data of mental health variables among health care workers represented as proportions or percentages. Two of these studies measured anxiety depression and stress symptoms, whereas three measured anxiety, depression, and insomnia, and four studies measured only anxiety and depression.

The first of these studies measured symptoms of anxiety, depression, insomnia among health care workers in Nepal during the first phase of pandemic (Khanal et al., 2020). A total of 475 Health care workers (HCWs) participated in the study through cross sectional web-based survey. The survey measured 41.9% of anxiety symptoms in health workers, whereas 37.5% had depression and 33.9% had insomnia like symptoms. 14-item Hospital Anxiety and Depression Scale (HADS) was used for Anxiety and depression while the 7-item Insomnia Severity Index (ISI) was used for Measuring Insomnia. Nurses had reported higher levels of anxiety symptoms than other health care workers (data referred from table 3).

The second study measured moderate levels of depression, anxiety, and other stress symptoms among frontline health care workers in Vietnam during the peak of Covid-19 pandemic (Than et al., 2020). Among 173 health care worker participants, the frequency of depression, anxiety and stress symptoms were 20.2%, 33.5%, and 12.7%, respectively. However, 12.1% had major PTSD symptoms and 20.2% had sleeping disorders. The Depression, Anxiety, and Stress Scale – 21 Items (DASS-21) was used to measure the perceived stress, anxiety, and depression symptoms. Impact of Event Scale – Revised (IES-R) and the Insomnia Severity Index (ISI) was used to assess the psychological distress and insomnia disorder (referred table 3).

The third study examined the correlation between religious coping, anxiety, and depression among health care workers during Covid-19 pandemic in Kuala Lumpur, Malaysia (Chow et al., 2021). In a total of 200 Health worker participants, the prevalence of anxiety and depression was 36.5% and 29.5%. Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety and depression among the participants. The Brief Religious Coping Scale (Brief RCOPE M) was used to measure the significant association of positive and negative religious coping with anxiety and depression. The positive religious coping and improving negative religious coping through cognitive therapy, religious counselling was found effective in improving mental health of health care workers in pandemic (referred table 3).

The fourth study aimed to evaluate the anxiety and depression symptoms among health care givers in the early stage of Covid-19 pandemic in Lagos, Nigeria (Erinoso et al., 2020). A total of 105 participants enrolled in a cross sectional structural self-reported questionnaire-based survey. Around 9.5% reported with mild anxiety, 3.8% moderate, 1.9 % severe anxiety while 12.4% had mild depression, 0.9% moderate and 2.9% had severe depression symptoms. 9-item patient health care questionnaire (PHQ-9) was used to measure the level of depression and 6-item Generalized Anxiety Disorder (GAD-6) was used to measure the level of anxiety. Frontline health care workers who spent longer time working in Covid-19 related capacity had higher odds of moderate to severe depression symptoms as compared to those who spent less time (referred table 3).

The fifth study as per referred table 3, examined the mental health of physicians or health care staff by evaluating the prevalence and association of anxiety and depression like potential risk factors in Bangladesh during Covid-19 pandemic (Khatun et al., 2021). The prevalence of anxiety among male and female health workers were 27.6% and 42.1%, while the rate of depression on male and female health care workers were 26.3% and 50%. 7-item Generalized Anxiety Disorder (GAD-7) scale and Nine-item Patient Health Questionnaire (PHQ-9) were used to measure the anxiety and depression among 114 front line (HCWs) participants. The study examined that the marital status, job location, and workload per day were risk factors for anxiety, while age, sex and marital status were risk factor for depression.

The sixth study in table 3 (study findings) measured the anxiety, depression, and stress among 112 (health care professionals) participants during Covid-19 pandemic condition in Karachi, Pakistan (Sandesh et al., 2020). 72.3% had suffered from moderate to extremely severe depression, 85.7% had

suffered from moderate to extremely severe anxiety and 90.1% had reported moderate to extreme stress levels. 21- item Depression Anxiety Scale (DASS-21) tool was used to measure the three negative emotional states which were anxiety, depression, and stress.

The seventh study examined the anxiety, depression, insomnia, and other psychological symptoms in health care workers (200) and non-health care workers (100) during lockdown or rapid spread of Covid-19 pandemic for complete duration of 3 months in India (Raj et al., 2020). The prevalence of anxiety was 55.65%, 48.54%, 52.34%, and 56% of physicians, nursing staff, technicians, and non-healthcare workers, while depression was reported from 32.1%, 53.72%, 42.7%, and 35% of the above-mentioned categories, respectively. The frequency of insomnia was 47%, 38.2%, 39.4%, and 43% and other psychological problems were found 43.51%, 41.9%, 28.3%, and 45% of the physicians, nurses, technical staff, and non-healthcare professionals. Generalized Anxiety Disorder scale and structural questionnaire was used to assess the anxiety, depression, and insomnia among participants (referred table 3).

The eighth study examined the symptoms of depression, anxiety, and stress among health care workers during peak of Covid -19 pandemic in three states of Pakistan (Multan, Lahore, and Faisalabad) (Arshad et al., 2020). The frequency of Depression, Anxiety and Stress (DAS) in the health care worker participants (n=276) was 10.1%, 25.4%, and 7.3%, respectively. Females were more depressed than males (female vs male: 6.47 ±2.77 vs 4.66 ±3.40, p <0.001). Whereas in comparison to males, the anxiety symptoms were more common among female HCWs (female vs male: 5.60 ±3.14 vs 4.51 ±3.35, p <0.001). Depression, anxiety, and stress scale (DASS-21) was used to measure anxiety, depression, and stress symptoms among participants (data given in table 3).

Finally, the last study aimed to examine the anxiety and depression symptoms and associated risk factors among physicians during Covid-19 outbreak in Bangladesh. A total of 412 Bangladeshi physicians were enrolled for cross sectional web-based surveys. The prevalence of anxiety and depressive symptoms among physicians was 67.72% and 48.5% respectively. The outcome assessed through Hospital Anxiety and Depression Scale (HADS) and Covid-19 related questionnaires. The risk factors for high rate of anxiety and depression among participants were found fear of being infected, low income, heavy workload, inadequate training, use of self-funded PPE (Personal Protective Equipment) and shortage of staff (referred table 3).

d) Risk of bias in individual studies

Risk of bias assessment for the cross -sectional studies was assessed using a tool by (Hoy et al., 2012). The grading criteria of the overall risk of bias for cross-sectional studies were based on the selection of population, sampling frame, randomization, non-response bias, data collection, case definition, reliability & validity, data collection mode and numerators & denominators. Out of nine studies eight studies had clearly specified population. And only one did not specify clearly about nonresponse bias. The sampling frame, settings and data collection, methods were described clearly. The prevalence and the outcomes were specified. Overall, the quality of the study was identified as low risk. The details are listed in table 4.

Table 2: Study characteristics of included studies

Records	First Author	Year	Journal/Conference	Country	City	Setting	study design	Population	Sample size(n)
1	Khanal,P	2020	Globalization and health	Nepal		Hospital based	Cross-sectional study	Health workers	475
2	Than, HM	2020	Risk Management & Healthcare Policy	Vietnam	Hanoi	Hospital based	Cross-sectional study	Health workers	173
3	Chow, SK	2021	NA	Malaysia	Kuala Lumpur	Hospital based	Cross-sectional study	Health workers	200
4	Erinoso, O	2020	Journal of Psychosomatic Research	Nigeria	NA	Hospital based	Cross-sectional study	Health workers	105
5	Khatun,M	2021	Frontiers in Public Health	Bangladesh	NA	Hospital based	cross-sectional study	health workers	114
6	Sandesh, R	2020	NA	Pakistan	NA	Hospital based	cross-sectional study	health workers	112
7	Raj, R	2020	Family Medicine and Primary Care	India	NA	Hospital based	Observational study	health workers	350
8	Arshad, M	2020	Psychology Research and Behavior Management	Pakistan	Multan, Lahore, and Faisalabad	Hospital based	Cross-sectional study	health workers	276
9	Tasdik, H	2020	NA	Bangladesh		Hospital based	Cross-sectional study	health workers	412

Note: we included either frontline or non-frontline health care worker

Table 3: Study Outcome of the study

S. N	Year	Male/ female	Age Distribution	Scale used/ measurement tools	Types of outcome	Severity of outcome
1	2020	Female:52.6% Male: 47.4%	28.20(±5.80) years	14-item Hospital Anxiety and Depression Scale (HADS) was used for Anxiety and depression while the 7-item Insomnia Severity Index (ISI) was used for Measuring Insomnia.	Anxiety Depression Insomnia	anxiety (borderline: 23.6% and abnormal: 18.3%). Similarly, 37.5% of the participants experienced symptoms of depression (borderline: 24% and abnormal: 13.5%). Likewise, symptoms of insomnia were prevalent in 33.9% of the participants (sub-threshold insomnia: 26.7%, moderateinsomnia: 5.7% and severe clinical insomnia: (1.5%).
2	2020	Female:68.2% Male:31.8%	median age is 31	The Depression, Anxiety, and Stress Scale – 21 Items (DASS-21) was used to measure the perceived stress, anxiety, and depression symptoms. Impact of Event Scale – Revised (IES-R) and the Insomnia Severity Index (ISI) was used to assess the psychological distress and insomnia disorder.	Anxiety Depression Insomnia and Psychological distress	The frequency of depression, anxiety symptoms, and stress, were 20.2%, 33.5%, and 12.7%, respectively. 12.1% had major PTSD symptoms and 20.2% had sleeping disorders.
3	2021	Male: 79 (39.5%) Female: 121 (60.5%)	31-40: 70.5 % 20-30: 25.5 %	HADS was used to assess anxiety and depression among the participants.	Anxiety and Depression	The prevalence of anxiety and depression was 36.5% and 29.5%.
4	2020	male: 48(45.7%) Female: 54(54.3%)	mean age is 34.5	9-item patient health care questionnaire (PHQ-9) was used to measure the level of depression and 6-item Generalized Anxiety Disorder (GAD-6) was used to measure the level of anxiety	anxiety and depression	anxiety level normal: 84.8% mild: 9.5% moderate:3.8% severe: 1.9% depression level normal: 83.8% mild: 12.4% moderate: 0.9% severe: 2.9%
5	2021	male:76 (66.7%) female: 38(33.7%)	mean age is 35	9-item Patient Health Questionnaire (PHQ-9) was used to assess the severity of depression and 7-item Generalized anxiety disorder (GAD-7) was used to assess the severity of anxiety.	anxiety and depression	the prevalence of anxiety among male and female were 27.6% and 42.1%, while the rate of depression on male and female were 26.3% and 50%.
6	2020	male:64 (57.1%) female: 48(42.9%)	NA	21- item Depression Anxiety Scale (DAS-21) tool was used to measure the three related negative emotional states, which are: anxiety, depression and stress.	anxiety, depression and stress	72.3% had suffered from moderate to extremely severe depression, 85.7% had suffered from moderate to extremely severe anxiety and 90.1% had reported moderate to extreme stress levels.
7	2020	Male:52% Female: 48%	mean age is 35	Generalized Anxiety Disorder scale used to	Anxiety Depression and	The prevalence of anxiety, depression, insomnia, and

				assess the anxiety, depression and insomnia among participants.	Insomnia	other psychological problems was found to be 46.04%, 44.37%, 28.75%, and 56.87%, respectively among participants.
8	2020	Male:182 (65.9%) Female:94 (34.1%)	26-30: 62.3% 30-40: 37.7%	Depression, anxiety, and stress scale (DASS-21) used to measure anxiety and depression among participants	Anxiety, Depression and stress symptoms.	The frequency of Depression, Anxiety and Stress in the Health care worker participants was 10.1%, 25.4%, and 7.3%,respectively. Females are more depressed than males (female vs male: 6.47 ±2.77 vs 4.66 ±3.40, p <0.001). While in comparison to males, the anxiety symptoms were more common among female HCWs (female vs male: 5.60 ±3.14 vs 4.51 ±3.35, p <0.001).
9	2020	Male:50% Female: 55 %	25-34: 76.2%	Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety and depression among the participants.	Anxiety and Depression.	The prevalence of anxiety and depressive symptoms among physicians was 67.72% and 48.5% respectively.

Table 4: Quality assessment Cross-sectional studies

Author	Year	Population	Sampling frame	Random selection	Non-response bias	Data collection	Case definition	Instrument's reliability and validity	Data collection mode	Numerators and denominators	Score	Overall risk of bias
Khanal,P	2020	0	0	0	0	0	0	0	0	0	0/9	Low risk
Than, HM	2020	0	0	0	0	0	0	0	0	0	0/9	Low risk
Chow, SK	2021	0	0	0	0	0	0	0	0	0	0/9	Low risk
Erinoso, O	2020	0	0	0	0	0	0	0	0	0	0/9	Low risk
Khatun,M	2021	0	0	0	0	0	0	0	0	0	0/9	Low risk
Sandesh, R	2020	1	0	0	0	0	0	0	0	0	1/9	Low risk
Raj, R	2020	0	0	0	0	0	0	0	0	0	0/9	Low risk
Arshad, M	2020	0	0	0	1	0	0	0	0	0	1/9	Low risk
Tasdik, H	2020	0	0	0	0	0	0	0	0	0	0/9	Low risk

0: Yes 1: No 0-3: Low risk 4-6: Moderate risk 7-9: High risk

Hoy et al tool questions

1. Was the study's target population a close representation of the national population in relation to relevant variables (e.g age, sex, occupation)?
2. Was the sampling frame a true or close representation of the target population?
3. Was some form of random selection used to select the sample, OR was a census undertaken?
4. Was the likelihood of non-response bias minimal?
5. Were data collected directly from the subjects (as opposed to a proxy)?
6. Was an acceptable case definition used in the study?
7. Was the study instrument that measured the parameter of interest (e.g prevalence of low back pain) shown to have reliability and validity (if necessary)?
8. Was the same mode of data collection used for all subjects?
9. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?

XII. Discussion

This analysis of HCW mental health across low and middle-income countries shows two key findings. First, at least one form of mental health outcome was prevalent across the nine different studies. Secondly, anxiety and depression were the common forms of mental health prevalent in health workers.

Covid 19 pandemic has affected health care systems around the world and especially low and the middle -income countries. The health care workers are facing several challenges from treating patients with covid 19 to oneself becoming high risk of getting the Virus. Covid 19 has possessed a unique challenge in our health care workforce that will not only not interrupt their regular duties but also affect their mental health status. The findings from our study indicates that the psychological impacts of covid 19 on the health professionals is considerable, with increased levels of anxiety, depression, insomnia and stress.

Majority of our studies explored that prevalence outcomes of mental health disorders is higher in females than male health care workers. Studies highlighted by (Arshad et al., 2020) and (Khatun et al., 2021) at Pakistan and Bangladesh revealed that psychological disorders were more prevalent among female population. On our findings the anxiety and depression level of female is very high which was stated in 4 countries, Nepal, Bangladesh, Pakistan, Malaysia and Vietnam. This is similar to the study findings of (Zhang et al., 2020) which revealed that female suffering from anxiety symptoms were 2.5 times greater than their counterparts. Along with it the findings are also similar to the findings of the systematic study done by (Vizheh et al., 2020) on 'The mental health of healthcare workers in the COVID-19 pandemic' which, mentioned that female care worker and nurses have high depressive and anxiety symptoms than male workers. (Vizheh et al., 2020).

(Khatun et al. 2021 and Arshad et al. 2020), these two studies out of nine studies included in the paper, showed that older (more than 35 years) health care workers or physicians had lower risk of experiencing depression or anxiety than the young (less than 35 years) health care workers, which is supported by study in Taiwan for prevalence of psychological adaptation in health care workers during outbreak of SARS (Su et al., 2007). Moreover, similar results were reported by previous web based cross sectional study in China during Covid-19 pandemic, which shows that anxiety symptoms were more likely to occur in younger health care workers than over or 35 years health care workers (Huang et al., 2020). However, two other studies out of 9 studies reported that younger participants and who were more aware about government incentives for health care workers were less likely to stressed than older participants (41-50 years or over 50 years) (Khanal et al. 2020 and Raj et al. 2020). Because they were more stressed with extended working hours and highly worried about passing the infection to their family members, similar study was also conducted on health care workers to analysis the psychological impact and coping strategies during covid-19 in China (Cai et al., 2020). Therefore, the results suggested that need to implement stress management programs or interventions for both young and older health care workers in order to manage their stress.

XIII. Strength and Limitations

PRISMA guidelines was used for analysis of the reports which was considered as the strength. In addition, the elaborated eligibility and search criteria, the total number of databases identified, and three independent reviewers to assess the validity and reliability of the report. Additionally, only cross- sectional studies were used for analysis which gives clear data presentation. Risk of bias assessment has very low score which makes this study a reliable one. However, our study is limited to investigating the impact of COVID 19 pandemic on the mental health of health workers in low and middle-income countries.

XIV. Policy Implications

The findings from this research indicate that despite the strategies implemented by low and middle-income countries such as screening, handwashing and use of personal protective equipment there is still need of some strategies that mitigate or prevent the impact of COVID-19 pandemic on the mental health of health-care workers. The mental health of health care workers is neglected which can be improved by considering vulnerable health care workers. All health care workers should be undertaken risk assessment and if possible, they should be deployed to the non-care-based roles. This study guides the leaders and practitioners for the implementation of early intervention to mitigate loss of health care workers. Also, this might be helpful for guiding the future researchers.

XV. Conclusion

This study found that frontline care workers are at high risk for developing mental health consequences during working in Covid-19 pandemic situation. We found that during providing care to Covid-19 patients care givers experienced high level of anxiety, stress, insomnia, and other mental health issues. Implementation of interventions or strategies can help to reduce the mental pressure of health care workers. Early interventions for health care workers, opportunistic screening for mental health disorders, treatment in both psychological and pharmacological modalities, meditation, reducing the length of shifts, and providing

proper mental health and support services may help to reduce the burden of mental health consequences among health care workers. The result of our evaluation "mental health impact of COVID-19 Pandemic on health care workers" will be disseminated through the presentation and workshops.

XVI. Communication and Dissemination

This research review will be published in the Torrens University Journals. Also, various workshops and building interpersonal relationships, partnership and identifying the people can be helpful for the rapid dissemination of information. This study guides the leaders and practitioners for the efficacy of the interventions. Also, this might be helpful for guiding the future researchers. The result of our evaluation "mental health impact of COVID-19 Pandemic on health care workers" will be disseminated through the presentation and workshops.

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Appendices

Annex I: Data source and search strategy

Keyword	PubMed	EBSCOhost	Google Scholar
Afghanistan OR Albania OR Algeria OR Angola OR Antigua OR Barbuda OR Argentina OR Armenia OR Azerbaijan OR Bangladesh OR Belarus OR Belize OR Benin OR Bhutan OR Bolivia OR Bosnia OR Herzegovina OR Botswana OR Brazil OR Burkina OR Faso OR Burundi OR Cabo Verde OR Cambodia OR Cameroon OR Central African Republic OR Chad OR China OR People's Republic of Colombia OR Comoros OR Democratic Republic of Congo OR Congo OR Costa Rica OR Côte d'Ivoire OR Cuba OR Djibouti OR Dominica OR Dominican Republic OR Ecuador OR Egypt OR El Salvador OR Equatorial Guinea OR Eritrea OR Eswatini OR Ethiopia OR Fiji OR Gabon OR Gambia OR Georgia OR Ghana OR Grenada OR Guatemala OR Guinea OR Guinea-Bissau OR Guyana OR Haiti OR Honduras OR India OR Indonesia OR Iran OR Iraq OR Jamaica OR Jordan OR Kazakhstan OR Kenya Kiribati OR Democratic People's Republic of Korea OR Kosovo OR Kyrgyzstan OR Lao People's Democratic Republic OR Lebanon OR Lesotho OR Liberia OR Libya OR North Macedonia OR Madagascar OR Malawi OR Malaysia OR Maldives OR Mali OR Marshall Islands OR Mauritania OR Mauritius OR Mexico OR Micronesia OR Moldova OR Mongolia OR Montenegro OR Montserrat OR Morocco OR Mozambique OR Myanmar OR Namibia OR Nauru OR Nepal OR Nicaragua OR Niger OR Nigeria OR Niue OR Pakistan OR Palau OR Panama OR Papua New Guinea OR Paraguay OR Peru OR Philippines OR Rwanda OR Saint Helena OR Samoa OR OR São Tomé and Príncipe OR OR Senegal OR Serbia OR Sierra Leone	950	950	625

OR Solomon Islands OR Somalia OR South Africa OR South Sudan OR Sri Lanka OR Saint Lucia OR Saint Vincent and the Grenadines OR Sudan OR Suriname OR Syrian Arab Republic OR Tajikistan OR Tanzania OR Thailand OR Timor-Leste OR Togo OR Tokelau OR Tonga OR Tunisia OR Turkey OR, Turkmenistan, OR Tuvalu, OR Uganda OR Ukraine Uzbekistan OR Vanuatu OR Venezuela OR Vietnam OR Wallis and Futuna OR West Bank and Gaza Strip OR Yemen OR Zambia OR Zimbabwe. ANDAND (Depression, OR Insomnia, OR Anxiety, OR Extreme mood changes, OR Dementia or Bipolar disorder OR Extreme forgetfulness OR Obsessive-compulsive disorder OR Post Traumatic Stress Disorder, OR Schizophrenia OR Stress OR Mental Health AND (fft[Filter]))) AND (Covid-19 OR SARS-COV-2 OR , Covid-19 Pneumonia OR Nobel covid-19 OR Novel-Coronavirus, , Covid -19 Infection, Covid 19 illness. AND (fft[Filter]))) AND (Health care worker' OR 'Health care providers' OR ' Wellness worker ' OR 'Nursing Assistant' OR 'Care worker' OR 'Health Care Assistant' AND Sort by: Publication Date			
Afghanistan OR Albania OR Algeria OR Angola OR Antigua OR Barbuda OR Argentina OR Armenia OR Azerbaijan OR Bangladesh OR Belarus OR Belize OR Benin OR Bhutan OR Bolivia OR Bosnia OR Herzegovina OR Botswana OR Brazil OR Burkina OR Faso OR Burundi OR Cabo Verde OR Cambodia OR Cameroon OR Central African Republic OR Chad OR China OR People's Republic of Colombia OR Comoros OR Democratic Republic of Congo OR Congo OR Costa Rica OR Côte d'Ivoire OR Cuba OR Djibouti OR Dominica OR Dominican Republic OR Ecuador OR Egypt OR El Salvador OR Equatorial Guinea OR Eritrea OR Eswatini OR Ethiopia OR Fiji OR Gabon OR Gambia OR Georgia OR Ghana OR Grenada OR Guatemala OR Guinea OR Guinea-Bissau OR Guyana OR Haiti OR Honduras OR India OR Indonesia OR Iran OR Iraq OR Jamaica OR Jordan OR Kazakhstan OR Kenya Kiribati OR Democratic People's Republic of Korea OR Kosovo OR Kyrgyzstan OR Lao People's Democratic Republic OR Lebanon OR Lesotho OR Liberia OR Libya OR North Macedonia OR Madagascar OR Malawi OR Malaysia OR Maldives OR Mali OR Marshall Islands OR Mauritania OR Mauritius OR Mexico OR Micronesia OR Moldova OR Mongolia OR Montenegro OR Montserrat OR Morocco OR Mozambique OR Myanmar OR Namibia OR Nauru OR Nepal OR Nicaragua OR Niger OR Nigeria OR Niue OR Pakistan OR Palau OR Panama OR Papua New Guinea OR Paraguay OR Peru OR Philippines OR Rwanda OR Saint Helena OR Samoa OR OR São Tomé and Príncipe OR OR Senegal OR Serbia OR Sierra Leone OR Solomon Islands OR Somalia OR South Africa OR South Sudan OR Sri Lanka OR Saint Lucia OR Saint Vincent and the Grenadines OR Sudan OR Suriname OR Syrian Arab Republic OR Tajikistan OR Tanzania OR Thailand OR Timor-Leste OR Togo OR Tokelau OR Tonga OR Tunisia OR Turkey OR, Turkmenistan, OR Tuvalu, OR Uganda OR Ukraine Uzbekistan OR Vanuatu OR Venezuela OR Vietnam OR Wallis and Futuna OR West Bank and Gaza Strip OR Yemen OR Zambia OR Zimbabwe.	4397491	40552379	2750000
Depression, OR Insomnia, OR Anxiety, OR Extreme mood changes, OR Dementia or Bipolar disorder OR Extreme forgetfulness OR Obsessive-compulsive disorder OR Post Traumatic Stress Disorder, OR Schizophrenia OR Stress OR Mental Health Filters: Full text Sort by: Publication Date	1956267	7214507	105000
Covid-19 OR SARS-COV-2 OR , Covid-19 Pneumonia OR Nobel covid-19 OR Novel-Coronavirus, , Covid -19 Infection, Covid 19 illness. Filters: Full text Sort by: Publication Date	111018	1200486	348000

Annex II: Prisma 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	27-30
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7,8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

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MicroRNAs as Potential Regulators of Docosahexaenoic Acid Benefits in Alzheimer's Disease

By Vic Shao-Chih Chiang

Abstract- Alzheimer's disease (AD) is a highly prevalent neurodegenerative disease that imposes a prodigious burden on the society. Docosahexaenoic acids (DHA) are known to be beneficial in AD, in part through their anti-inflammatory properties. MicroRNAs (miRs) are important regulators of brain functions and this regulation becomes disrupted in AD.

Objectives: The purpose of this article is to propose the involvement of miRs in the anti-inflammatory effects of DHA on AD.

Methods: The literature surrounding this topic is extensively researched: miR involvement in the pathophysiology of AD, the mechanism of action of DHA, the effects of DHA on miRs and potential future therapeutic strategies for AD involving miRs.

Results: AD results in a disrupted miR network that relates to inflammation, but the altered miRs vary between studies. The effects of DHA on AD are generally positive but the mechanism remains enigmatic. Emerging studies demonstrate that one of the potential mechanisms of action of DHA is modulation of miRs.

Keywords: Omega-3; Diet; Anti-inflammatory; Inflammation; Nutrigenetics; Food-derived microRNA; Exogenous microRNA.

GJMR-K Classification: NLMC Code: WT 155

Strictly as per the compliance and regulations of:

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Discussion: Future AD studies investigating miRs needs to set experimental standards to enable valid comparisons. For DHA effects on AD, thorough considerations on the properties of the DHA and the population involved is necessary. Validation is required to verify miR involvement in the anti-inflammatory properties of DHA in the context of AD. The proposed miR-related strategies against AD remain to be substantiated.

Keywords: Omega-3; Diet; Anti-inflammatory; Inflammation; Nutrigenetics; Food-derived microRNA; Exogenous microRNA.

I. Introduction

Sporadic Alzheimer's disease (AD) is the age-related neurodegeneration leading to memory impairments, sensory and locomotive dysfunctions, apathy, aggression and eventually leading to splanchnic and peripheral system failure due to diminished networks within the central nervous system (CNS).[1]

Currently, one in nine elderlies above 65 years of age in the United States (US) has AD, excluding casesof preclinical AD.[2] For elderlies above 85 years of age, this prevalence becomes as high as one in three. AD is proposed to be the third leading cause of death in the US.[3] It administers a heavy burden on the society which reaches approximately $200 billion in the US every year.[4] With the forecast of AD affecting more than 100 million people worldwide by 2050, AD will create a significantly greater burden on the society.[4]

The etiology of AD is multifactorial and several hypotheses have been proposed including aberrant amyloid precursor processing into neurotoxic amyloid beta (Aβ) metabolites, hyper-phosphorylation of the microtubule-stabilizing protein tau, apoptotic alterations of synaptic operations and mitochondrial dysfunction-mediated neurotoxicity.[5,6]

There is also significant evidence that supports an inflammatory hypothesis for AD.[7,8] This inflammation is likelyto be both the cause[9,10] and the consequence[11,12] of AD. Microglia are macrophages for the CNS and they are found to be excessively activated in AD.[13] Inflammation appears to be an important trigger of this phenomenon.[13] This activation leads to further microglial release of pro-inflammatory mediators which creates a vicious self-perpetuating inflammation cycle that exacerbates AD.[13]

Currently approved pharmacotherapies of AD include the use of cholinesterase inhibitors (e.g. rivastigmine) and N-methyl-D-aspartate antagonist (e.g. memantine) to counteract neurotransmission impairments.[14] However these pharmacotherapies only slow the progression but do not cure AD. Many other AD pharmacotherapies are being developed and investigated but most fail during clinical trials. Therefore, there remain major demands for any strategies that can prevent, retard, halt or cure AD.

Dietary modifications offer key strategies against ADas observed from beneficial dietary effects from vitamins, phytochemicals, Mediterranean diet and Souvenaid®.[15-18] In contrast, diet may also exacerbate AD, as witnessed for high-fat diets and excessive intake of food contaminated with metals such as cadmium, lead and arsenic.[15,19]

Due to the underlying inflammation in AD, anti-inflammatory strategies have exhibited promising strategies against AD such as the use of non-steroidal anti-inflammatory drugs and anti-tumor necrosis factor alpha (TNFA) from human observational studies and animal trials.[8] Docosahexaenoic acid (DHA) is well-

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established for its anti-inflammatory properties and it has been observed in the literature to improve AD.[20] However, its mechanism of action remains enigmatic. Recent evidence suggests potential involvements of the important post-transcriptional gene regulator, microRNAs (miRs).[21]

II. MicroRNAs

MiRs were first identified in 1993 by the Ambros and Ruvkun laboratory from *Caenorhabditiselegans* experiments.[22] They were then identified to be conserved phylogenetically across the plant and animal kingdoms which then triggered a revolution in these newly classified non-coding RNAs.

For intergene- or exon-derived miRs, their canonical biogenesis pathway initiates with nuclear transcription of miR-coding genes into primary miR. [23] Cleavage via the microprocessor complex then occurs to form precursor miR (pre-miR), which is transported into the cytoplasm via exportin5. Dicer cleavage leads to the formation of mature double stranded miR duplex, that is incorporated into the RNA-induced silencing complex (RISC), followed by the degradation of the passenger strand. This is slightly different for intron-derived miRs and other emerging non-canonical miR biogenesis pathways are being increasingly recognized.[24]

The most well-known function of miRs are its gene-silencing effects on messenger RNA (mRNA) through Watson-Crick interactions between themiR 5'seed sequence nucleotides and the mRNA 3'untralslated region (3'UTR).[23] This leads to either repression of protein translation or degradation of the mRNA transcript. Only partial complementarity is required for gene-silencing effects and therefore single miR can target multiple mRNAs and vice versa. The presence of "isomiRs"[23] and other miR functions[25] further adds to the conundrum of miRs.

The regulation of miRs themselves are extremely complex and far from being understood. They can be regulated through changes in the miR biogenesis components, at the transcription level (transcriptional factors), the post-transcriptional level (pre-miR degradation and modification) as well asat the post-translational level (miR turnover and endogenous sponge activity).[24]

Some of these miRs have been determined to be specifically expressed or enriched in certain tissues. For the brain, a number of enriched miRs include *miR-128, miR-129, miR-133a, miR-138, miR-153, miR-181a, miR-181b, miR-218, and miR-219*.[24] Within neurons, there appears to be an enrichment of *miR-125b, miR-128, miR-32, miR-134* and *miR-139* in the synaptic and dendritic regions compared to the soma.[24]

MiRs have been reviewed to play essential roles in the development and proper functioning of the brain.[26] At the molecular level, miRs are involved in the lineage determination, maturation, survival and neurotransmission.[24] A troika of *miRs,miR-134, miR-132* and *miR-138* were recently reviewed for their imperative functions in neurons including dendritogenesis, morphogenesis, neuron plasticity, synapse formation, dendritic spine size, cell migration and axon regeneration.[27] They also participate in the in the differentiation, activation and polarization of microglia.[28] Using dicer knockout experiments, miRs have shown to be crucial for memory formation within the brain.[29] This is further supported by recent research that *miR-34a* and *miR-132* as well as *miR-138* regulate memory in rats and humans, respectively.[30,31] These pivotal roles of miRs conveys their profound potential as paramount strategies against AD.

III. The Roles of MicroRNAs in Alzheimer's Disease Inflammation

MiRs are known to participate in human AD, and the studies conducted to date are summarized in Table 1. *(Insert Table 1 here)* The roles of miRs in AD have been reviewed previously.[32] The present review discusses newer studies conducted since the earlier review and reinforces the anti-inflammatory aspects as a proposal for novel strategies against AD. Since inflammation is implicated in AD and miRs are known to participate in inflammation,[33] it is feasible to hypothesize some of the dysregulated miRs in ADare related to inflammation. From the clinical AD and miR studies conducted to date, several miRs were found to be differentially expressed in multiple studies. Some of these have shown to relate with inflammation and presents opportunities for counteracting the inflammation etiology underlying AD.

Table 1: Clinical studies on microRNA expression in Alzheimer's disease

Author	Clinical Samples	Up-regulated microRNA[1]	Down-regulated MicroRNA[1]
Wang et al. (2008)[85]	Cerebral cortex n=6		miR-103; miR-107; miR-23b
Hebert et al. (2008)[43]	Anterior temporal cortex n=5	miR-520h; miR-197; miR-511; miR-320; miR-516-3p;	let-7i; miR-22; miR-93; miR-26b; **miR-9**; miR-488; miR-363; **miR-181c**; miR-106b; miR-101; miR-210; **miR-15a**; miR-19b; miR-29b;
Sethi&Lukiw (2009)[40]	Temporal lobe neocortex n=6	**miR-9**; miR-125b; **miR-146a**	
Nunez-Iglesias et al. (2010)[44]	Parietal lobes n=5	miR-185; miR-382; miR-432; miR-486; miR-19790; miR-28648; miR-572; miR-18895; miR-35456; miR-320; miR-134; miR-45605; miR-10939; miR-10912; miR-617; miR-30184; miR-671; miR-188; miR-06383; miR-765; miR-575; miR-23974; miR-601;	miR-374; miR-582; miR-05109; miR-12504; miR-12497; miR-30e-5p; miR-376a; miR-44608; **miR-181c**; miR-368; miR-95; miR-20546; miR-148b; miR-02532; miR-42448; miR-101; miR-20b; miR-08570; miR-29b; **miR-15a**; miR-130a; miR-29c; miR-598; miR-494;
Shioya et al. (2010)[86]	Frontal lobes n=7		miR-29a
Geekiyanage& Chan (2011)[45]	Frontal cortices n=7		miR-137; **miR-181c**; **miR-9**; miR-29a; miR-29b-1; **miR-15**; miR-124
Long et al. (2012)[87]	Frontal cortex n=5		miR-153
Lau et al. (2013)[35]	Hippocampus n=41	let-7i-5p; let-7f-5p; miR-195-5p; miR-150-5p; miR-223-3p; miR-92b-3p; miR-362-3p; miR-23a-3p; miR-199a-3p; miR-199b-3p; miR-363-3p; miR-142-3p; **miR-27a-3p**; miR-200a-3p; miR-455-5p;	miR-409-5p; miR-370; miR-769-5p; **miR-132-3p**; miR-128; miR-138-5p; miR-129-5p; miR-433; miR-124-3p; miR-329; miR-425-5p; miR-127-3p; miR-487b; miR-129-2-3p; miR-487a; miR-543; miR-136-5p; miR-410; miR-495-3p; miR-219-2-3p;
Wong et al. (2013)[36]	Temporal cortex n=6		**miR-132**; miR-212
Bekris et al. (2013)[38]	Cerebellum n=21	miR-138; miR-208b; **miR-181c;** miR-152; miR-126; miR-330-3p; miR-184; miR-191; miR-328; miR-342-3p; miR-370; miR-501; miR-331-3p; miR-139-5p; miR-149; **miR-132;** miR-98; miR-204;	
Bekris et al. (2013)[38]	Hippocampus n=21	miR-138; miR-208b; **miR-181c;** miR-152; miR-126; miR-330-3p; miR-191; miR-328; miR-342-3p; miR-370; miR-501; miR-331-3p; miR-139-5p; miR-149; **miR-132**; miR-98; miR-204; **miR-15a**;miR-346; miR-221	miR-184
Absalon et al. (2013)[34]	Temporal cortex n=6	miR-26a; miR-26b; let-7i; miR-125b; miR-134; **miR-27a**; **miR-27b**; miR-29c; miR-30a-5p	**miR-132**
Muller et al. (2014)[41]	Hippocampus n=5		miR-16; miR-107; miR-128a; **miR-146a**

[1]The inflammation-related miRs that are discussed specifically in the review are bolded.

a) *miR-132*

MiR-132 has been consistently found to be down-regulated.[34-36] Further work in some of these studies discovered phosphatasetens in homolog (PTEN), forkhead box *(FOX)* O3a, *FOXO1a* and *p300* as its direct targets.[35,36] These genes participates in the inflammation-related phosphoinoinositide 3-kinase pathway (PI3K).[37]

(Wong et al., 2013) demonstrated a -3.8 fold change in *miR-132* within their Braak VI stage AD patients.[36] However, *(Lau et al., 2013)* found a more diminished *miR-132* down-regulation of approximately -1.6 fold.[35] The robustness of the results from *(Lau et al., 2013)* study is greater due to higher statistical significance ($p<0.00001$) and verification of their nCounter miR data (Nanostrings) with locked-nucleic acids (Exiqon) quantitative real time polymerase chain reaction (qPCR).[35]

Disagreement was presented by *(Bekris et al., 2013)* where they found *miR-132* to be up-regulation in AD.[38] However, their study failed to divide samples into Braak stages and adopted inappropriate age-matched controls. Furthermore, their results did not persist following TaqManqPCR (Applied Biosystems) validation.

b) *miR-146a*

MiR-146a has been described extensively as an inflammation-related miR.[39] It was identified to be up-regulated in earlier studies,[40] but observed to be down-regulated in a more recent study.[41] It regulates nuclear factor kappa B (NFKB), which is a vital pro-inflammatory transcription factor.[42]

The disparity between these two AD studies may arise from the difference in the tissues used, where *(Muller et al., 2014)*[41] profiled only the hippocampus but *(Sethi & Lukiw, 2009)*[40] profiled the whole temporal lobe neocortex. In addition to that, it was shown by *(Muller et al., 2014)*[41] that there was actually an up-regulation of *miR-146a* at Braak III, followed by a decrease in Braak VI.

Since *(Sethi & Lukiw, 2009)*[40] did not provide Braak staging for their AD patients, *(Muller et al., 2014)* contributes to more valuable *miR-146a* changes that allows its surveillance across different Braak stages within AD.[41]

c) *miR-15a*

The up-regulation of *miR-15a* in AD was determined[38], but contrasting results were identified in earlier studies [43-45]. *MiR-15a* is validated to target inflammation-related genes including peroxisome proliferated-activated receptor *(PPAR)*-delta[46] and coactivator-associated arginine methyltransferase 1[47].

Studies that found *miR-15a* down-regulation revealed a -1.5 magnitude with statistical significance $p<0.01$, based on microarray (LC Sciences & Ambion) data.[43,44] Comparatively, the methodology used by *(Bekris et al., 2013)* was more robust in that they had three phases of miR screening using TaqManqPCR (Applied Biosystems) and normalization to three housekeeping genes.[38] Although, valid comparison was further complicated by the use of different brain sections in these studies as well as the absence of considerations for Braak staging.

d) *miR-181c*

Down-regulation of *miR-181c* was detected in three AD studies.[43-45] It was shown to be up-regulated in the preliminary screening by *(Bekris et al., 2013)*, but their statistics were not significant enough to proceed to the third stage validation of this study.[38] *MiR-181c* has been reviewed in terms of its involvement in inflammation in aspects of their regulatory roles on immunosenesence, T cells activity and mitochondrial encoded cytochrome c oxidase 1.[48]

Within the AD studies that found *miR-181c* down-regulation, the resulting magnitudes were discrepant.[43-45] This is likely attributable to the use of different brain tissues as well as RNA extraction methodology. In terms of the miR profiling, two of these studies adopted a microarray (LC Sciences & Ambion) approach but did not proceed with conventional qPCR validation.

(Geekiyanag & Chan) practiced a comparatively more robust methodology with quantification using singleplexmiScriptqPCR (Qiagen) and their AD cohort being more defined to specifically profile samples at Braak V.[45] They found a -2.5 fold change within the frontal neocortex.

e) *miR-27*

Up-Regulation of miR-27 was recognized in two of the AD miR studies with similar fold changes around 1.7.[34,35] It was ascertained in other literature to target the anti-inflammatory genes. *IL-10* and *PPARG* expression.[49,50]

Since the Braak stages in AD patients investigated by *(Absalon et al., 2013)*[34] were only at Braak III, and *(Lau et al., 2013)*[35] at Braak VI, this may lead to the perception that *miR-27* change occurs at an early stage of AD. Nonetheless, several differences between these two studies prohibit this inference to be made. Variations exist for their brain sections profiled, sample size and miR profiling methods.

While *(Lau et al., 2013)*[35] had a much greater sample size of 41 and extra miR purification steps, the confirmation of *miR-27* up-regulation found in their nCounter miR assay (Nanostrings) failed to persist with miRCURY locked nucleic acid qPCR (Exiqon) validation.

f) *miR-9*

Two studies demonstrated *miR-9* down-regulation.[43,45] It has been revealed to activate microglia through NFKB signaling[51] and targeting PPARD[52].

(Geekiyanage & Chan, 2011)[45] found higher down-regulation of -3.3 compared to -1.3 found by *(Hebert et al., 2008)*[43]. As mentioned previously, the methodology presented by *(Geekiyanage & Chan, 2011)*[45] has higher credibility. Albeit, differences may likewise derive in that the temporal cortex was profiled by *(Hebert et al., 2008)*[43] in contrast to the frontal neocortex used by *(Geekiyanage & Chan, 2011)*[45].

No gold standard currently exists for miR work,[53] and therefore the comparison between AD miR studies are difficult. This can be further complicated by the discrepancies in the use of brain sections, Braak stages, ethnicity, genotypes, [54] gender and polymorphisms in miR target sites.[32,54] Nevertheless, these provide valuable grounding for future research.

It is equally important to validate the inflammation-related mRNAs targeted by the differentially expressed miRs in future AD studies to facilitate development of anti-inflammatory strategies against AD.

IV. The Effects of Docosahexaenoic Acids Onalzheimer's Disease

Docosahexaenoic acids (DHA) are well known for its anti-inflammatory properties.[55] It is along chain omega-3 polyunsaturated fatty acid (n3) made up of 22 carbons and 6 cis double bonds in a homoallylic arrangement.[56] The brain is made up of 60% lipids and 15% of these are DHA, which implicates its essential roles within the brain. Since n3 cannot be synthesized *de novo*, they must be obtained from external sources such as seafood or in the form of alpha linolenic acid (ALA) within certain plant foods.[55]

ALAundergoes elongase and desaturase-mediated metabolism into eicosapentaenoic acid (EPA) and then into DHA.[55] They can then be carried across the endothelial cells lining the blood brain barrier via MFSD2A[57] and then esterified into phospholipids at the stereospecific number-2 position[55]. Its liberation from neuronal membranes can be made via phospholipase to mediate intracellular anti-inflammatoryactions by inhibiting activity of NFKB. Current hypotheses of these actions are proposed to involve the docosanoid pathway via lipoxygenase conversion into resolvins, protectins and maresins[58] or the activation of G-coupled protein receptor 120 and PPARG[55]. DHA is also important for neuronal membrane fluidity, long term memory, neurotransmission and synaptic plasticity.[55]

A systematic review concluded from meta-analysis of 18 observational studies, that n3 was beneficial for AD.[59] Furthermore, higher levels of direct n3 biomarkers in the elderly were associated with superior brain white matter, [60] less executive decline[61] and generally positive brain characteristics[20]. In addition, a meta-analysis of animal trials with directn3 supplementation revealed improvements of AD-related pathophysiologies including reduced Aβ, diminished neuronal loss and improved cognitive function.[62] In contrast to these, in a recent meta-analysis of 34 human clinical trials, n3 did not benefit cognition or AD in the elderly.[63]

The inconsistency of these results may emanate from differences in the n3 consumed in terms of the food source, food processing and form of supplementation. These disparities can all alter the chemistry of n3 such as its isomerism, homoallylic arrangement, oxidation and stereospecific numbering.[56] Oxidized n3 can lead to development of various diseases through damage to physiological systems and 62% of marketed n3 supplements have been found to be significantly oxidized.[64] As described earlier, the population used within the study is also paramount and supplementation at later stages of AD appeared to be less effective.[55] These are key considerations for newer n3 clinical trials, but decades of evidence do suggest DHA to be beneficial for the CNS. Through elucidation of the underlying miR mechanism, anti-inflammatory strategies of DHA against AD can be optimized.

V. The Effects of Docosahexaenoic Acids on Micrornas

MiR studies investigating dietary modifications in the CNS are extremely exiguous and none of these are directly relevant to AD. With regards to the relationship between DHA and miR, only eight published studies exist and these findings are summarized in Table 2. The effects of DHA on miR have been reviewed partially in 2012, but many more miR studies of DHA have been generated since then.[65]

Table 2: Docosahexaenoic acid effects on microRNA expression

Author	Model	Up-regulated microRNA	Down-regulated MicroRNA
Davidson et al. (2009)[66]	Sprague-Dawley rats colon (induced colon tumour by azoxymethane)	Let-7d; miR-15b; miR-107; miR-191; miR-324-5p	
Farago et al. (2011)[67]	GBM2 Glioma cells	miR-143	miR-30c; miR-145

Farago et al. (2011)[67]	GBM5 Glioma cells	miR-20b	miR-22; miR-30c; miR-143; miR-145
Farago et al. (2011)[67]	U373 Glioma cells	miR-145	miR-22
Shah et al. (2011)[88]	Sprague-Dawley rats colon (induced colon tumour by azoxymethane)		miR-19b; miR-27b; miR-497; miR-93; miR-18a; miR-203; miR-26b
Mandal et al. (2012)[89]	Mice breast cancer tumour		miR-21
Mandal et al. (2012)[89]	Breast cancer cells (MCF-10A, MDA-MB-231, MCF-7)		miR-21
Baselga-Escudero et al. (2013)[90]	Dyslipidemic rats liver		miR-33a; miR-122
Gil-Zamoranoet al. (2014)[91]	Caco-2 cells	let-7e; let-7f; miR-1283; miR-330; miR-374b; miR-658; miR-1; miR-221-3p; miR-181a-5p; miR-141-3p; miR-143-3p; miR-191-5p; miR-29b-3p; miR-192; miR-30c	miR-30a
Siddesha et al. (2014)[92]	Primary mouse cardiac fibroblasts (treated with Ang II)		miR-21
Antal et al. (2014)[21]	Glioma cells U87 MG (treated with radiation)	miR-146; miR-181a	

Most of these were addressed in other physiological systems with only two conducted within the CNS. These studies in other physiological systems still provide relevant insights to potential miR mechanisms in DHA anti-inflammatory effects on AD. For example, one study illustrated an up-regulation of *miR-107* and their further validation revealed the amyloid processing enzyme, beta-secretase 1, as amiR-107 target.[66]

a) Farago et al., 2011Study[67]

In this CNS study, the highly fatal malignant glioma was investigated.[67] Their study explored the effects of multiple PUFAs, including DHA based on previous literature evidence that these can combat gliomas. Their aim was to elucidate the miR mechanism of DHA action on gliomas.

For this, they treated glioblastoma cells (U373, GBM2, GBM5) with 50 & 100 μM DHA for 24 hours and then extracted for their miR (Roche). The miRs were profiled using a megaplexTaqManqPCR (Applied Biosystems) followed by further validation with singleplexTaqManqPCR (Applied Biosystems). They also quantified levels of selected apoptotic mRNA targets that were predicted for the differentially expressed miR using qPCR.

The only miR that was found to change in all three cell lines was *miR-145*, but the direction of change was discrepant for U373. This suggests possible specificity of DHA action on different cell lines. This notion is further supported by disparities in the magnitude of *miR-145* change between GBM2 of -1.5 fold with GBM5 of -4.7 fold. Therefore, it would be more appropriate to discuss these cell lines separately.

In GBM2, other miRs that were altered include down-regulation of *miR-30c* and up-regulation of *miR-143*. Down-regulation of *miR-22*, *miR-30c* and *miR-143* were discovered for GBM5 as well as up-regulation of *miR-20b*. In U373, aside from the *miR-145* up-regulation, *miR-22* was found to be down-regulated.

In terms of the mRNA targets, correlation was made to their complementary miR. Successful inverse relationships were found for *miR-20b* with tumor protein p53 inducible nuclear protein 1 *(TP3INP1)*, *miR-22* with sirtuin 1 *(SIRT1)*, *miR-30c* with integrin, beta3 *(ITGB3)*, *miR-143* with v-Ki-ras2 oncogene *(KRAS)* and prostaglandin-endoperoxide synthase 2 (*COX2*) as well as *miR-145* with insulin receptor substrate 1 *(IRS1)*. These miR associations with apoptotic genes suggest DHA involvement in apoptosis, which is closely related with inflammation.[68]

b) Antal et al., 2014 Study[21]

This CNS study was conducted by the same research group and they again investigated glioma but this time they focused on DHA enhancement of radiotherapy against glioma cells.[21] The mechanism of this radiotherapy enhancement by DHA remains enigmatic and therefore the researchers intended to determine the miR mechanism to optimize radiotherapy against glioma.

They subjected U87 glioblastoma cells under 10Gy cobalt irradiation and then treated with 25μM DHA for 48 hours. RNA was extracted from cells (Bioneer) and selected miR expression were quantified using singleplexTaqManqPCR (Applied Biosystems). Candidate mRNAs were similarly quantified using qPCR.

The combination of DHA with radiation did not alter any of the miRs that were measured (*miR-34a; miR-96; miR-146; miR-181a; miR-148a; miR-148b* and *miR-152)*, but DHA alone up-regulated miR-146a and *miR-181a*. With DHA treatment alone, it was sufficient to pose significant negative effects on U87 cells. In the case of mRNAs, they found up-regulation of oxidative stress related genes including anti-inflammatory heme oxygenase (decycling) 1) *(HMOX1)* and pro-apoptotic NAD(P)H dehydrogenase, quinone 1 *(NQO1)*. Genes related to endoplasmic reticulum (ER) stress were also altered encompassing the pro-survival G protein-coupled receptor 78 *(GPR78)* and pro-apoptotic DNA-damage-inducible transcript 3 *(DDIT3)*. Early growth response protein 1 *(EGR1)* is an early-response gene in radiotherapy that coordinates cell differentiation and growth. It was up-regulated with DHA treatment. The Notch signaling pathway was likewise altered through up-regulation of *NOTCH1*. Despite validation of direct *miR-146a* and *miR-181* targets were not performed in this study, the up-regulation of multiple genes indicates probable involvement of these miRs in these pathways. Many of these pathways including oxidative stress, ER stress and Notch signaling are known to relate with inflammation.[69]

Portions of the DHA-regulated miRs similarly correspond to miRs that were altered in AD (Table 1). Some of these have also been discussed earlier to engage in inflammation including *miR-15, miR-27, miR-181* and *miR-146*. Aside from these inflammation-related miRs already discussed, some of the other DHA-regulated miRs are likewise known to associate with inflammation. These includes RECK, lipid metabolism, oncology and stress pathways.[70,71] Through this elucidation of DHA anti-inflammatory mechanisms, they offer valuable insight as strategy against AD.

The two studies described demonstrate the potential for DHA to affect miR expression within CNS. While they do provide beneficial preliminary intuition, the cell specificity of DHA effects[72] signifies the importance of establishing their effects on AD-related neuronal and neuroglial miR expression.

The objective to investigate their underlying anti-inflammatory mechanism in AD requires thorough considerations. For *in vitro* studies, the considerations for AD-relevant cell lines or primary cells are necessary. As described above, the parameters of the DHA supplemented is equally important. Furthermore, the miR methodology demands the adoption of robust procedures that are comparable to high quality studies. Animal models and human studies will also be useful. As addressed above, regards need to be paid for the characterization of AD patients, brain section that is profiled and sample size.

VI. How MicroRNAs Contribute to Future Strategies against Alzheimer's Disease

By understanding miRs that are responsible for anti-inflammatory effects of DHA on AD, improvements can be made to existing tactics as well as development of novel strategies. The first miR therapy is presently being tested under clinical trial to explore *miR-34* replacement as an anti-tumor therapy.[73]

Exogenous miRs offer possible solution where exogenous miR transfer from dietary origin was first documented in 2012 that discovered the presence of rice-derived miRs in human serum.[74] It is feasible for miRs to survive gastrointestinal digestion due to their well-appreciated stability.[75] This property is ascribed to their selective cellular export into various transport mechanisms.[75,76] The extracellular miRs can then be taken up by recipient cells to mediate function distally.[75,77,78]

Newer studies further support food-mediated miR transfer into human, porcine and murine biological fluids from plants and milk.[79-81] By contrast, there are similarly studies that refute this notion as shown in bees, mice, macaques and human.[82,83] The presence of miRs from other species have been recently reported to possibly arise from undesirable contamination or arte facts of sequencing methodologies.[84] Based on these arguments, dietary transfer of miRs remains to be concluded. Additional considerations needs to be made whether the amount of exogenous miR transferred translate into biological significance. Nevertheless, these demonstrate the feasibility of using exogenous miRs as strategies against AD.

The concept of exogenous miR supplementation for AD requires knowledge of miR mechanisms of how DHA antagonizes AD inflammation. The miRs that are responsible can be supplemented to create novel food products or nutraceuticals. Genetic engineering can likewise be adopted to enhance levels of these miRs within foods. In an alternative perspective, the efficiency of miR-modulation by DHA in AD can be enhanced through understanding which aspects of the DHA molecule (e.g. unsaturation, stereospecificity,

allylism) are responsible for its anti-inflammatory effects. This can lead to fabrication of optimized DHA and derivatives to maximize their miR effects to antagonize AD inflammation.

AD is afflicted with a pathological state of inflammation and this can be counteracted through anti-inflammatory effects of DHA. They underlying mechanism likely involves miRs and through its elucidation, novel strategies can be developed to combat AD. AD is highly prevalent, affecting 1 in 3 elderlies above 85 years of age. It is the third leading cause of death in United States and attributes to a financial burden of $200 billion annually. Any prevention, retardation, termination or reversal strategies against AD will reduce the significant and rapidly growing societal burden attributed by AD.

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Reproductive Performance of Bonga Sheep under Community based Breeding Program: The Intermediate Result

By Metsafe Mamiru, Sandip Banerjee, Aynalem Haile & Asrat Tera

Abstract- The aim of this paper is to point up some reproductive parameters of Bonga sheep under farmer's management in Adiyo-kaka district. A total of 3270 newborn lambs recorded between 2009 and 2013 GC in Boka-shuta farmers' cooperative is used for this study. Data of reproductive performance concerning some traits are analyzed by descriptive analysis, while the remaining are presented on a percentage basis. Results comprise the findings from the reproductive studies on Bonga ewes and lambs over five years (2009-2013). The lambing interval (LI) and age at first lambing (AFL) of Bonga sheep were 8.5±1.6 and 14.6±2.5 months respectively, while annual reproductive rate, litter size, and lifetime lambing of the ewes were 1.9, 1.37, and 11.4 heads, respectively. The performance of the sheep breed was encouraging in general. However, traits like AFL and LI were longer and still need to be shortened for reproductive efficiency. Therefore, we recommend further within breed selection among the flock for desired reproductive traits to achieve a higher lamb crop with superior performance.

Keywords: *bonga sheep, on-farm, performance, adiyo kaka, Ethiopia.*

GJMR-K Classification: *NLMC Code: QY 54*

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Metsafe Mamiru [α], Sandip Banerjee [σ], Aynalem Haile [ρ] & Asrat Tera [ω]

Abstract- The aim of this paper is to point up some reproductive parameters of Bonga sheep under farmer's management in Adiyo-kaka district. A total of 3270 newborn lambs recorded between 2009 and 2013 GC in Boka-shuta farmers' cooperative is used for this study. Data of reproductive performance concerning some traits are analyzed by descriptive analysis, while the remaining are presented on a percentage basis. Results comprise the findings from the reproductive studies on Bonga ewes and lambs over five years (2009-2013). The lambing interval (LI) and age at first lambing (AFL) of Bonga sheep were 8.5±1.6 and 14.6±2.5 months respectively, while annual reproductive rate, litter size, and lifetime lambing of the ewes were 1.9, 1.37, and 11.4 heads, respectively. The performance of the sheep breed was encouraging in general. However, traits like AFL and LI were longer and still need to be shortened for reproductive efficiency. Therefore, we recommend further within breed selection among the flock for desired reproductive traits to achieve a higher lamb crop with superior performance.

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I. Introduction

Sheep play an important role in the rural economy of Ethiopia (Kosgey, 2007), but productivity of the breeds in the country is among the poorest in sub-Saharan Africa. Thus, attempts have been made to improve the productivity of local breeds through crossbreeding with imported genotypes (Tibbo, 2006), however, there have been little efforts to select indigenous breeds for improved productivity, including reproduction.

Hence, a community-based breeding program was established for four sheep breeds representing different agro-ecologies and production systems in Ethiopia to improve native breeds through within breed selection. Bonga sheep is one of the sheep breeds which have been considered for community-based production in Ethiopia. The breed has got priority as it was known for its high growth rate and prolificacy. Bonga sheep reared in the areas where mixed crop-livestock production system practiced is characterized by the long fat tail and highly preferred for meat production. The breed is classified as a large size breed and can thrive in places where disease and internal parasites are obstacles to production (Zewdu, 2008). Thus, emphasis was given to explore the genetic potential of the sheep breed concerning mutton production through undertaking performance testing of the breed.

Thus, on-farm recording of traits of economic importance that encompasses reproduction and production attributes has been taking place since 2009. Major attributes measured were body weight (at birth, weaning, and six months), the number of lambs weaned and the number of lambs born, birth date, birth type (single/twin), neonatal deaths and sex. However, the collected data regarding the phenotype of reproductive traits of ewes were not analyzed.

Reproductive performance is a trait of outstanding importance in sheep production enterprises. Reproductive performances of sheep together with survival and growth traits, are determinants of productivity of sheep in meat livestock farming systems (Wilson et al., 1985). Reproductive efficiency in a prime lamb producing ewe flock is a key driver of profitability (Cottle, 2010), and lamb survival is known to be a key component of reproductive efficiency. (Hinch & Brien, 2014).

Reproductive performance is measured by several parameters. The most commonly used ones are the proportion of lambs born (alive and dead) per ewe lambing (also called drop rate and a measure of prolificacy), and age at first lambing. Also lambing percentage (number of lambs born per ewe exposed to the ram); and weaning percentage (percentage of lambs weaned per ewe exposed to the ram) although the latter is more of an economic measure. To measure lamb losses, it is preferable to calculate stillbirth rates and pre-weaning mortality rates as a proportion of lambs born and lambs born alive, respectively. Therefore, the aim of this paper is to point up some reproductive parameters of Bonga sheep under farmer's management.

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II. Materials and Methods

a) Description of the study area

The study was conducted in Adiyo-Kaka district of Kaffa zone, particularly in Boka kebele, where farmers are organized into cooperatives with the objective of improving Bonga sheep breed through participatory selection. The area is placed to the Southwestern part of the country in Kafa zone. Natural forest covers large area of the district, and the area is known by growing bamboo tree (*Yushania alpina*) (Metsafe et al., 2017). The district is situated within a longitude of 36° 47"E and a latitude of 7° 26"N with an altitude ranging from 500 to 3500 meters. The temperature in the area can be as high as 36°C and can also reach the lowest value of 3°C (SUDCA, 2007). The known farming system of the area is mixed crop-livestock production. It has a livestock population of 107657, 30819, 28825, 47176, and 7699 cattle, sheep, goat, chicken, and equines, respectively (report of Agricultural and rural development office of Kafa zone, 2012).

b) Sampling procedure and source of data

We selected the study area purposely due to the existence of a community-based breeding program (CBBP) for Bonga sheep in the area. The source of data for this particular study was secondary data from the record book of enumerators. We used the performance data of 3270 lambs born over five years (2009-2013) to evaluate the reproductive performance of the sheep breed. Data for the study were different reproductive parameters gathered by the purposely recruited enumerators since 2009 G.C.

c) Data management and analysis

Outliers were screened and removed from the data before conducting the main data analysis. Descriptive analysis was employed to determine the overall performance of the sheep breed concerning some traits. These stands for reproductive characters like lambing interval, age at first lambing and lifetime lambing. Other parameters like pre-weaning mortality, twinning rate, litter size, annual reproductive rate, and survivability/mortality rate were computed on a percentage basis using their respective formulas below.

ARR= LS (1-M)/LI ---------- (1)

Where

ARR- Annual Reproductive Rate

LS - Litter size

M- Pre weaning mortality rate

LI - Lambing interval (Ibrahim, 1998)

Litter size= number of lambs born/number of ewes lambing X100% ---------- (2)

Pre-weaning mortality rate = no. of lambs died/total number of lambs born X100% ---------- (3)

Weaning rate = no. of lambs weaned/total number of ewes lambing X100% ---------- (4)

Pre-weaning survival rate = no. of lambs weaned/total no. of lambs born X100% ---------- (5)

III. Result

a) Reproductive performance of Bonga sheep

The Boka-shuta farmers' cooperative recorded a total of 3270 newborn lambs between 2009 and 2013 GC. The reproductive performance of the sheep breed is summarized in Table 1. The results indicated that the number of ram lambs born was higher than the ewe lambs in the study area. The proportion of ram lambs is 53.49% out of 3270 lambs. Accordingly, female to male ratio of the lambs was 1:1.15, which varies from the expected ratio (1:1). The weaning rate, twinning rate, and mortality rate of the sheep breed were 118.8%, 34.9%, and 13%, respectively. In contrast, the litter size/prolificacy (LS) and annual reproductive rate (ARR) of Bonga sheep were 3.7 and 1.9 heads, respectively. Bonga ewes give birth to about 11.4 lambs on average in their lifetime with the average age at first lambing and lambing interval 14.6 (438 days) and 8.5 (255 days) months, respectively.

Table 1: Frequency and descriptive statistics of reproductive traits for Bonga sheep

Parameters	Mean± SE
Lambing interval (LI)**	8.5±1.6
Age at 1st lambing (AFL)**	14.6±2.5
Number of lambs born/ewes lifetime*	11.4±0.1
Pre-weaning mortality rate (%)	13
Weaning rate (%)	118.8
Twinning rate (%)	34.9
Sex ratio (F:M)*	1:1.15
Litter size (LS)*	1.37
Annual reproductive rate*	1.9

**-in heads, **-in months, %-percent, SE-Standard Error*

IV. Discussion

a) Reproductive performance

The lambing interval (LI) obtained in the present study (8.5±1.6) was comparable with the value reported by Fikirte (2008) for sheep in Damot-Gale woreda. However, it is slightly longer than the value reported by Belete (2009) to the same breed (Bonga sheep). The differences observed may be attributed to changes in management of the sheep in the study area. It is highly accredited to the shortage of grazing areas due to increased demand of land for crop cultivation. Solomon (2007), and Fisehatsion (2013) also reported shorter lambing intervals for Gumuz sheep and sheep in Gamogofa zone, respectively. However, longer LI than the current finding was reported by Samuel (2005) for sheep breed in Ada‟‟a woreda.

Both genetic and environmental factors (nutrition, post-weaning growth, and disease and parasite infestation) influence the age at first lambing (AFL); thus, the trait can have wide variation both within a breed and production systems (Getahun, 2008; Girma, 2008). Age at first lambing found in this study was presented in Table 1. The values are in agreement with the values reported by Niftalem (2000) for Menz sheep. However, it was longer than the values reported by Tsedeke (2007), Getahun (2008), Belete (2009), and Fisehatsion (2013). In contrary, it is shorter than reports by Adugna (1998), and Samuel (2005) for sheep raised in Kochere and Ada''a woredas respectively. Following a better nutritional plan for earlier maturity and thus for earlier age at puberty could help to shorten the AFL.

Both genetic and environmental factors influence the LS of various sheep breeds in tropics such as Garole breed from West Bengal in India (Banerjee et al., 2011). Many tropical and temperate breeds (Davies et al., 2002) carry several fecundity genes and they result variation in prolificacy. Embryonic mortality and reabsorption during different stages of pregnancy (due to intrauterine competition of the fetus for nutrients and space) are some of the non-genetic factors influencing the trait (Hammond et al., 1984). The average litter size of Bonga sheep mentioned in Table 1 was within the range (1.08 and 1.75) reported for tropical breeds (Girma (2008). It is also in agreement with previous reports of Solomon (2000) and Zewdu (2008) for Horro and Bonga sheep, respectively. Tsedeke (2007), Zewdu (2008), and Belete (2009) reported higher LS than the present result for Arsi-Bale, Horro, and Bonga sheep breeds kept in village conditions, respectively. However, Armbruster and Peters (1993), Niftalem (2000), Asmamaw and van Arendonk (2006), and Mengistie (2009) reported lower LS than the current finding for Djallonke, Menz, Horro, and Washera sheep breeds, respectively.

The annual reproductive rate (ARR) best estimates the impact of reproduction on sheep and goat productivity. The average ARR of African sheep breeds was 1.2 (Mukasa and Lahlou 1995), while Gaten by (1986) and Wilson (1989) reported the value to be 1.4 for Menz sheep reared in highlands of Ethiopia. The ARR value of 1.9 lambs per head (Table 1) in the current study, is much higher than values reported by the mentioned authors. The observations might be the fallout of lower mortality rate and high level of prolificacy in the breed. The value reported in the present study is also much higher than the ARR of 0.89 for Alaba sheep described by Tsedeke (2007). The current result is within the range of 0.89-1.97 heads reported elsewhere in the tropics (Wilson, 1989). The same author reported 0.82 heads of the traitfor Yatenga sheep in Sub Saharan Africa, which is lower than the present result. The higher ARR indicates that there may be specific genes influencing prolificacy, and fecundity in the breed. Hence, it is important to identify the genetic factors (if any for the high ARR). A study by Davis (2004) identified that the presence of FecB gene in heterozygous form increases the ovulation in Booroola Merino by 1.5, while it improves the ovulation by about 3.0 times if the gene is homozygous.

The average mortality rate found in the present study (13%) was lower than 13.9% reported by Deribe (2010) for Adilo sheep. It is also much lower than the mortality rate (20.9%) reported by Belete (2009) in Southwest Ethiopia. Berhanu (2006) reported the pre-weaning mortality rate of 15% for Menz sheep, which is higher than the present result. Decline of the pre-weaning mortality rate presently might be due to better management. Metsafe (2015) stated that, restriction of lambs to run with their mothers at an earlier stages, better health management, and frequent vaccination all contributed to the lower death of lambs. The low mortality rate observed might also be attributed to the tolerance of the breed to some commonly occurring ovine diseases.

The twinning percentage of Bonga sheep breed obtained in the study was 34.9%, which is lower than those of Horro (39.9%) and Bonga (36.0%) sheep breeds previously reported by Zewdu (2008). Unintentional selection against twin bearers as practiced by the producers might be the reason for the lower twinning rate currently in the area. Table 1 summarizes the female to male ratio of lambs in the study area. It is slightly lower than the female to male ratio (1:0.91) of Adilo sheep (Deribe, 2010). According to the resource allocation theories (Cheryl and Michael, 2004), the higher percentage of ram lambs than ewe lambs indicates better nutrition and care of the ewes, especially during the gestation period.

Long-term reproductive performance (longevity, high fertility, ability to produce more lambs) under harsh environment is one of the adaptation traits of tropical livestock (Kosgey et al., 2007). The average lifetime lamb production found in the study is lower than 13.5

lambs reported by Solomon (2008) for Gumuz sheep. It is also lower than 12.2 and 15.3 lambs per head for Bonga and Horro sheep reported by Zewdu (2008). However, the low number of lambs in ewe's lifetime (10.3 and 7.9) than the current result is described by Dejen (2010) in Kafa and Bench Maji zones, respectively.

V. Conclusion and Recommendation

From the study, it is concluded that the overall performance of the sheep breed was legitimately promising in general. However, traits like AFL and LI were longer and still need to be shortened for reproductive efficiency and the subsequent productivity. Specifically, the higher annual reproductive rate (ARR) obtained in the study is an indication that there may be specific genes influencing prolificacy, and fecundity in the breed and hence it is important to identify the genetic features (if any). Generally, it is suggested that further selection among the flock for desired reproductive traits to achieve higher volume of lamb with superior performance is essential.

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Wild Honey Poisoning: A Case Report from Remote Mountains

By Santosh Adhikari & Abhishek Bhandari

Abstract- Wild honey is consumed as a tonic in different parts of the world with a belief of increasing libido and treating various musculoskeletal, gastrointestinal and cardiovascular symptoms. However, honey produced from the nectar of several species of the Ericaceae (Rhododendron) family may contain grayanotoxins which act on sodium ion channels and place them in partially open state which causes symptoms like sweating, dizziness and altered sensorium owing to their effect on cardiac muscles and nervous system. We report a case of 60 years male who consumed wild honey as a pain reliever and later presented to the emergency room of Manang District Hospital with bradycardia, hypotension and altered mental status.

Keywords: *wild honey, grayanotoxins.*

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Wild Honey Poisoning: A Case Report from Remote Mountains

Santosh Adhikari [α] & Abhishek Bhandari [σ]

Abstract- Wild honey is consumed as a tonic in different parts of the world with a belief of increasing libido and treating various musculoskeletal, gastrointestinal and cardiovascular symptoms. However, honey produced from the nectar of several species of the Ericaceae (Rhododendron) family may contain grayanotoxins which act on sodium ion channels and place them in partially open state which causes symptoms like sweating, dizziness and altered sensorium owing to their effect on cardiac muscles and nervous system. We report a case of 60 years male who consumed wild honey as a pain reliever and later presented to the emergency room of Manang District Hospital with bradycardia, hypotension and altered mental status.

Keywords: wild honey, grayanotoxins.

I. Introduction

Wild Honey hunting is an old age tradition in Manang and other Himalayan parts of Nepal. Historically, wild honey has been used for gastritis, peptic ulcer disease, hypertension, wound healing, common cold, and diabetes. Studies have suggested about the possible health benefits of honey as an antihypertensive [1], antidiabetic, antioxidant [1], cardioprotective [2], antitussive and anti-bacterial [3]. However honey poisoning is caused by the consumption of wild honey (mad honey) made by bees from certain species of rhododendron [4]. Grayanotoxin is a naturally occurring sodium channel toxin found in honey made by bees from the pollen and nectar of the Ericaceae family of the Rhododendron [5]. Grayanotoxin binds the voltage-dependent sodium (Na) channel from the cytoplasmic side of excitable cells in human body in its open state after binding to the receptors preventing inactivation of Na channel and thus, increases the membrane permeability of Na channels. As a result, the membrane hyperpolarizes and leads to increase in refractory period. This leads to decrease in firing rates of pacemaker cells in the heart and decrease in cardiac contractility [6]. Thus, hypotension and bradycardia are the most common physical finding. Cardiac arrhythmias including sinus bradycardia (commonest), nodal rhythms and atrioventricular block are the usual electrocardiographic findings [7]. This report details a case of accidental wild honey poisoning presented with bradycardia and hypotension and its successful management in the emergency room.

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II. Case Report

A 60-year male without any past comorbid illness, presented in the emergency unit of Manang District Hospital, Chame, Manang, Nepal with history of ingestion of wild honey about 200 ml in amount. After around 1 hour of ingestion, the patient had multiple episodes of vomiting containing ingested food particles, generalized tingling, burning sensation, dizziness and altered sensorium. The patient had consumed the honey as a musculoskeletal pain reliever following physical exertion. On presentation to emergency, the patient was ill looking with Glasgow Coma Scale of 12 (E3M4V5) and was vomiting. The patient had blood pressure of 70/50 mm of Hg, heart rate of 52 beats/minute, axillary temperature of 97^0 Fahrenheit, respiratory rate of 22 breaths per minute and capillary oxygen saturation of 85% in room air. Immediate twelve lead ECG showed sinus bradycardia with rate of 50 beats per minute (Figure 1). All the laboratory investigations including hemoglobin, total leukocyte count, differential leukocyte count, serum sodium, potassium, urea and creatinine and serum level of liver enzymes were within normal range (Table 1).

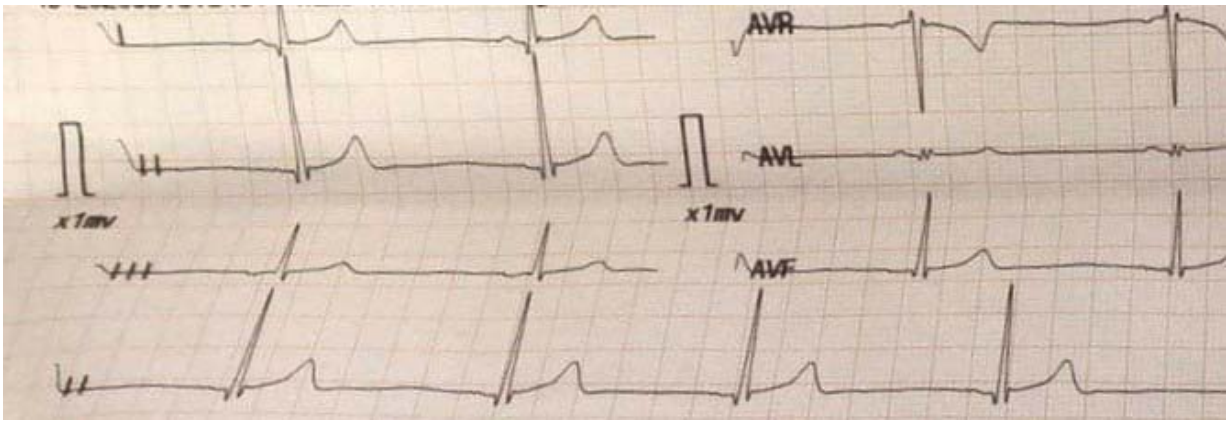

Figure 1: Electrocardiogram showing sinus bradycardia.

Table 1: Value of lab parameters.

Lab Parameters (units)	Value at admission
Total Leukocyte Count (cells/mm^3)	8100
Differential Leukocyte count (% of Total Leukocyte count)	Neutrophil 65% Lymphocyte 35%
Hemoglobin (g/dl)	13.2
Serum urea (mg/dl)	25
Serum Creatinine (mg/dl)	0.7
Serum Sodium (mmol/L)	140
Serum Potassium (mmol/L)	3.8
Serum Total Bilirubin (mg/dl)	1.2

The patient was provided with supplemental oxygen at the rate of 2l/min, given bolus intravenous crystalloids at 20ml/kg within one hour and was kept in Atropine infusion to maintain mean arterial pressure above 65 mmHg and heart rate above 50 beats per minute. The patient was kept nil per oral and received maintenance fluid at 80 ml/hour, injectable proton pump inhibitor and antiemetic. After about one hour of treatment, the Glasgow Coma Scale of the patient improved to 15/15. Atropine infusion was withheld after 8 hours of hospital stay, and his heart rate normalized to 70 to 75 beats per minute and twelve-lead electrocardiography showed normal sinus rhythm which persisted throughout hospital stay. The patient also made adequate urine output of 60 ml per hour over this time and continued to do so during hospital stay. Symptoms of vomiting also subsided over this time. The patient was discharged after 48 hours of observation in medical ward without complications.

III. Discussion

Grayanotoxins are found in leaves and flowers of plants of the family Ericaceae including *Rhododendron, Agarista and Kalmia* genera [8] which are available in Manang and other hilly regions of Nepal [9]. Grayanotoxin binds to the voltage gated sodium channels which prevents inactivation of the channels and increases their membrane permeability leading to hyperpolarization. The toxic effects of grayanotoxin are rarely fatal and usually last for not more than 24 hrs. Generally, they induce symptoms of dizziness, weakness, perspiration, salivation, nausea, vomiting and signs of hypotension, bradycardia, atrioventricular block and syncope [10].

In our patient, symptomatic emergency care with appropriate fluids and low dose atropine improved altered mental status, hypotension and bradycardia within short period of time. Patient with acute coronary syndromes can also present with similar symptomatology but with ischemic changes in ECG, serum positivity for cardiac injury biomarkers and vessels abnormality in coronary angiogram. Similarly organophosphate poisoning with cholinergic excess can also present with similar signs and symptoms with deranged cholinesterase enzyme activity on laboratory analysis.

Estimation of cholinesterase enzyme level in serum can be done to rule out organophosphate poisoning, which has a quite similar manifestation of cholinergic excess. The enzyme level is not affected by mad honey poisoning [11]. However, in the rural setup like ours, such laboratory analysis and cardiac catheterization facility are unavailable. Patient's history of consumption of wild honey along with suggestive ECG is ultimate for diagnosis.

Hunting and consumption of wild honey is a traditional and common practice in Manang and other Himalayan parts of Nepal. However, proper studies have not been done in these parts about the presence of toxic components in the plants which are available in this region belonging to the Ericaceae family. Also, the studies illustrating the therapeutic uses of such plants not available. These sort of accidental poisoning warrants such studies and creation of awareness among residents of areas where wild honey consumption practice is common. Also, with timely intervention and observation, patient presenting with this poisoning can be treated with readily available drugs with good prognosis. Physicians working in areas with wild honey hunting and consumption tradition should be aware of this poisoning.

Conflict of Interest: None.

Consent: Case Report Consent Form was signed by the patient and the original article is attached with the patient's chart.

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Comparison of Performance and Competitive Performance Judoists Ii (13-14 Years) and III (15-17 Years) Age Groups

By A.M. Mamytov & O.V. Koptev

When an athlete moves from stage to stage, it is very important to know which indicators change reliably. So it is possible to identify the leading indicators of readiness and competitive activity, on which coaches should focus their attention [1, 2]. The age of 13-14 corresponds to the stage of in-depth specialization, 15-17 years - to the stage of sports improvement. At the age of 15-17, the main parameters of an adult athlete are formed. Therefore, the identified indicators will remain the main ones until the end of their sports career.

Keywords: judo; competitions; preparedness of sportsman; fight.

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Comparison of Performance and Competitive Performance Judoists Ii (13-14 Years) and III (15-17 Years) Age Groups

СРАВНЕНИЕ ПОКАЗАТЕЛЕЙ ПОДГОТОВЛЕННОСТИ И СОРЕВНОВАТЕЛЬНОЙ ДЕЯТЕЛЬНОСТИ ДЗЮДОИСТОВII (13-14 ЛЕТ) И III (15-17 ЛЕТ) ВОЗРАСТНЫХ ГРУПП

A.M. Mamytov [α] & O.V. Koptev [σ]

При переходе спортсмена с этапа на этап очень важно знать какие показатели изменяются достоверно. Так можно выявить ведущие показатели подготовленности и соревновательной деятельности, на которых тренерам стоит сосредоточить своё внимание[1, 2]. Возраст 13-14 лет соответствует этапу углубленной специализации, 15-17 лет – этапу спортивного совершенствования. В 15-17 лет формируются основные параметры взрослого спортсмена. Поэтому выявленные показатели останутся главными до конца спортивной карьеры.

Ключевые слова: дзюдо; соревнования; подготовленность спортсмена; схватка.

When an athlete moves from stage to stage, it is very important to know which indicators change reliably. So it is possible to identify the leading indicators of readiness and competitive activity, on which coaches should focus their attention [1, 2]. The age of 13-14 corresponds to the stage of in-depth specialization, 15-17 years - to the stage of sports improvement. At the age of 15-17, the main parameters of an adult athlete are formed. Therefore, the identified indicators will remain the main ones until the end of their sports career.

Keywords: judo; competitions; preparedness of sportsman; fight.

Для определения различий в показателях соревновательной деятельности и тестирования дзюдоистов двух возрастных групп было проведено их сравнение по t-критерию Стьюдента.

Сравнение с испытуемых15-17 лет веса до 46 кг испытуемых 13-14 летвеса до 35 кг выявило различия в следующих показателях: объемах соревновательной (X2, X3), эффективной (X4, X5) и проигранной (X6, X7)техник, соревновательной эффективности защиты (X9), интервалах атаки (X10, X11), качественной надежности защиты (X14, X15), техничности (X16), показателе преследований в борьбе лёжа (X17), комбинационности атакующих действий стоя (X18), показателе контратакующих действий стоя (X19), коэффициенте асимметрии техники стоя (X20), результате показанной эффективности (X21), соревновательной компетентности (X22), метаниях теннисного (X23) и толканиях набивного (X24) мяча в цель, отжиманиях в упоре лёжа в течение 15-ти секунд (X26), прыжке в длину с места (X28), подтягиванияхв висе (X29), двухминутном беговом тесте для оценки общей выносливости (X31), скорости двигательной реакции (X32, X34), интеллектуальном тесте Малиновского С.В. (X35). По большинству показателей преимущество у спортсменов III группы; кроме X6, X11, X31, X32, X34. Естественно, и соревновательная компетентность (X22) в этой группе достоверно выше и составляет 36,43%; а во II группе – 29,83% (Таблица).

Сравнение с этой же выборкой испытуемых II группы веса до 38 кг выявило, что у них достоверно выше такие показатели: ОПТЛ (X7), СЭА (X8), Иа (X10), Иуа (X11), КНАС (X12), КНАЛ (X13), ППБЛ (X17), общая выносливость (X31). У спортсменов III группы: ОСТС (X2), ОСТЛ (X3), ОЭТЛ (X5), СЭЗ (X9), КНЗС (X14), КАДС (X18), ПКАДС (X19), КАТС (X20), бег на 60 м (X25), сгибания туловища до прямого седа в течение 20-ти секунд (X27), прыжок в длину с места (X28), подтягивания в висе (X29), приседания с партнером собственного веса (X30), скорость сложной двигательной реакции (X33), тест Малиновского С.В. (X35), оценка выполнения 10-ти бросков через спину (X37). Таким образом, по уровню различных видов подготовленности спортсмены III группы значительно превосходят спортсменов II группы, что вполне естественно, учитывая возраст и стаж занятий дзюдо. Однако в СД у II группы достоверно выше коэффициенты атаки (X8, X10 - X13); а также коэффициенты, характеризующиеборьбу лежа (X7,X17). У III группы достоверно выше коэффициенты, характеризующие технический арсенал (X2,

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Таблица: Сравнение показателей дзюдоистов II (13 - 14 лет) и III (15 - 17 лет) групп

Группа, вес	X2	X3	X4	X5	X6	X7	X8	X9	X10	X11
Xср. (III, 46 кг)	8,86	1,71	2,14	0,71	1,86	0,29	16,36	87,81	41,56	281,09
m	0,29	0,13	0,16	0,08	0,11	0,05	0,73	0,75	1,31	10,40
Xср. (II, 35 кг)	4,17	0,00	1,17	0,00	1,50	0,50	16,15	68,89	47,77	172,71
m	0,19	0,00	0,10	0,00	0,06	0,06	1,48	1,78	1,64	6,66
P ≤	0,001	0,001	0,001	0,001	0,01	0,01		0,001	0,01	0,001
Xср. (II, 38 кг)	6,43	0,57	2,14	0,43	1,57	0,14	28,23	82,34	35,28	199,29
m	0,22	0,06	0,13	0,06	0,10	0,04	1,79	1,27	1,03	17,86
P' ≤	0,001	0,001		0,01		0,05	0,001	0,001	0,001	0,001
Xср. (II, 42 кг)	6,14	1,00	1,57	0,43	1,57	0,00	18,33	82,03	39,46	193,20
m	0,28	0,09	0,12	0,06	0,08	0,00	1,09	1,58	1,43	12,17
P'' ≤	0,001	0,001	0,01	0,01	0,05	0,001		0,001		0,001
Xср. (II, 46 кг)	6,88	1,25	2,88	0,88	1,88	0,38	28,76	79,35	33,59	142,85
m	0,29	0,09	0,17	0,07	0,12	0,08	1,35	1,58	0,91	8,50
P''' ≤	0,001	0,01	0,01				0,001	0,001	0,001	0,001
Xср. (III, 50 кг)	9,30	2,10	3,70	1,50	1,80	0,40	27,19	83,15	33,60	139,08
m	0,20	0,08	0,17	0,09	0,11	0,06	1,12	1,40	0,79	6,13
Xср. (II, 50 кг)	7,13	0,50	1,88	0,13	1,25	0,38	23,69	80,26	61,22	483,93
m	0,32	0,06	0,13	0,04	0,07	0,05	2,20	1,53	1,60	68,91
P ≤	0,001	0,001	0,001	0,001	0,001				0,001	0,001
Xср. (III, 55 кг)	9,00	1,29	2,65	0,82	2,06	0,71	19,86	83,71	32,62	185,84
m	0,36	0,10	0,20	0,10	0,12	0,07	0,81	0,99	0,93	8,65
Xср. (II, 55 кг)	9,88	1,50	3,00	0,50	2,38	1,00	18,36	81,27	32,14	167,94
m	0,50	0,14	0,18	0,08	0,14	0,08	1,12	0,85	0,56	6,60
P ≤				0,01		0,01				
Xср. (III, 60 кг)	8,08	1,83	3,17	0,92	2,33	0,25	25,85	86,50	36,05	163,87
m	0,38	0,10	0,19	0,07	0,09	0,05	1,20	0,88	0,97	7,14
Xср. (II, 60 кг)	6,33	0,56	2,33	0,33	1,89	0,11	27,85	77,39	33,19	118,29
m	0,15	0,06	0,17	0,05	0,12	0,04	1,63	1,20	1,06	5,81
P ≤	0,001	0,001	0,001	0,001	0,01	0,05		0,001	0,05	0,001

Примечание- P', P'', P''' - различия между дзюдоистами III группы веса до 46 кг и II группы веса до 38, 42, 46 кг соответственно.

Продолжение таблицы

Группа, вес	X12	X13	X14	X15	X16	X17	X18	X19	X20	X21	X22
Xср. (III, 46 кг)	1,20	2,01	9,06	7,26	5,98	6,85	15,33	12,34	60,13	59,76	36,43
m	0,07	0,15	0,09	0,52	1,14	0,75	1,87	1,86	2,75	2,40	1,37
Xср. (II, 35 кг)	1,39		8,17	3,57	1,42	2,49	8,33	3,98	78,57	45,83	29,83
m	0,13		0,13	0,32	0,20	0,47	2,12	0,83	2,60	3,52	1,78
P ≤			0,001	0,001	0,001	0,001	0,01	0,001	0,001	0,001	0,01
Xср. (II, 38 кг)	2,00	5,21	8,53	7,43	6,46	22,10	2,86	0,00	71,88	52,14	40,89
m	0,16	0,54	0,11	0,65	1,34	1,35	0,80	0,00	3,49	3,27	1,96
P' ≤	0,001	0,001	0,001			0,001	0,001	0,001	0,01		
Xср. (II, 42 кг)	1,46	2,54	8,45	9,90	2,01	7,77	5,56	2,50	79,21	56,90	33,41
m	0,10	0,30	0,13	0,00	0,25	0,84	1,02	0,43	1,87	1,94	1,82
P'' ≤	0,05		0,001	0,001	0,001		0,001	0,001	0,001		
Xср. (II, 46 кг)	2,02	5,91	8,21	7,92	2,63	5,50	2,04	11,39	77,31	61,47	41,02
m	0,08	0,41	0,19	0,35	0,25	0,53	0,61	1,55	1,86	1,51	0,72
P''' ≤	0,001	0,001	0,001		0,01		0,001		0,001		0,01
Xср. (III, 50 кг)	1,91	5,03	8,88	7,90	15,28	7,84	5,84	5,84	66,48	70,40	49,54
m	0,07	0,30	0,09	0,27	3,82	0,87	0,61	0,74	2,48	1,68	0,90
Xср. (II, 50 кг)	1,92	0,93	8,48	4,95	1,34	22,79	5,91	4,17	63,49	56,01	27,57
m	0,19	0,23	0,15	0,56	0,13	1,97	0,92	1,24	1,37	2,74	1,35
P ≤		0,001	0,05	0,001	0,001	0,001				0,001	0,001
Xср. (III, 55 кг)	1,47	5,11	8,98	5,24	3,40	7,18	8,19	13,21	77,10	60,35	43,78
m	0,08	0,50	0,06	0,46	0,46	0,88	0,99	1,13	1,27	1,75	0,91
Xср. (II, 55 кг)	1,36	2,19	8,88	4,18	1,12	3,16	4,65	9,53	70,45	49,70	35,22
m	0,08	0,28	0,06	0,38	0,07	0,38	0,76	0,71	2,65	1,28	1,30
P ≤		0,001			0,001	0,001	0,01	0,01	0,05	0,001	0,001
Xср. (III, 60 кг)	1,82	3,23	8,92	8,49	2,78	9,60	4,56	8,96	64,40	70,76	42,19
m	0,08	0,22	0,07	0,27	0,19	0,95	0,67	1,06	2,21	1,26	0,94
Xср. (II, 60 кг)	1,97	5,44	8,22	4,95	2,46	2,24	6,84	5,49	77,08	58,41	38,47
m	0,14	0,68	0,12	1,20	0,28	0,52	1,16	1,01	1,84	2,52	1,53
P ≤		0,01	0,001	0,01		0,001		0,05	0,001	0,001	0,05

Продолжение таблицы

Группа, вес	X23	X24	X25	X26	X27	X28	X29	X30	X31	X32	X33
Xср. (III, 46 кг)	3,60	3,29	9,76	19,00	18,29	186,71	13,43	18,14	0,54	84,71	164,86
m	0,11	0,15	0,09	0,67	0,37	2,28	0,81	1,04	0,02	1,40	2,71
Xср. (II, 35 кг)	2,63	2,50	9,57	17,00	18,83	168,67	7,67	16,33	0,35	80,17	167,67
m	0,12	0,16	0,07	0,60	0,42	1,43	0,33	1,01	0,02	1,00	2,01
P ≤	0,001	0,001		0,05		0,001	0,001		0,001	0,01	
Xср. (II, 38 кг)	3,41	3,57	10,06	18,71	17,14	170,29	5,86	14,14	0,37	82,29	174,71
m	0,10	0,10	0,08	0,46	0,44	1,73	0,30	0,71	0,01	1,31	2,11
P' ≤			0,05		0,05	0,001	0,001	0,01	0,001		0,01
Xср. (II, 42 кг)	3,09	2,86	9,81	18,00	18,71	175,43	6,57	16,29	0,33	89,71	168,14
m	0,11	0,17	0,10	0,46	0,42	1,85	0,49	0,91	0,01	1,42	2,46
P'' ≤	0,001					0,001	0,001		0,001	0,01	
Xср. (II, 46 кг)	2,69	2,38	9,78	15,88	19,00	194,63	5,50	11,88	0,35	85,63	186,38
m	0,11	0,19	0,07	0,66	0,48	2,64	0,44	0,60	0,01	1,56	3,39
P''' ≤	0,001	0,001		0,001		0,05	0,001	0,001	0,001		0,001
Xср. (III, 50 кг)	2,92	3,10	9,26	20,30	18,80	196,70	11,20	27,80	0,44	86,40	168,10
m	0,10	0,13	0,06	0,87	0,37	1,86	0,59	1,60	0,01	1,04	2,65
Xср. (II, 50 кг)	3,65	3,25	9,56	15,75	19,25	193,25	5,63	23,13	0,35	88,25	173,75
m	0,06	0,13	0,07	0,64	0,45	2,46	0,28	1,41	0,01	1,97	2,82
P ≤	0,001		0,001	0,001			0,001	0,05	0,001		
Xср. (III, 55 кг)	3,09	2,88	9,49	18,71	19,00	196,76	13,18	26,94	0,38	87,59	165,47
m	0,10	0,14	0,08	0,54	0,41	2,75	0,63	1,27	0,01	1,28	3,06
Xср. (II, 55 кг)	3,03	2,88	9,40	17,38	20,63	200,38	8,50	24,13	0,28	91,00	182,75
m	0,12	0,19	0,09	0,54	0,41	2,90	0,33	0,60	0,01	1,69	3,03
P ≤					0,01		0,001	0,05			0,001
Xср. (III, 60 кг)	3,32	2,58	9,16	22,83	22,33	202,25	16,25	29,92	0,35	87,08	164,08
m	0,09	0,13	0,08	0,57	0,66	2,14	0,46	1,41	0,01	1,03	2,51
Xср. (II, 60 кг)	3,11	2,67	8,93	21,44	20,11	201,00	8,44	15,33	0,33	88,89	175,44
m	0,11	0,17	0,08	0,94	0,85	2,14	0,57	0,95	0,01	1,68	3,07
P ≤					0,05		0,001	0,001			0,01

X3, X5, X20), защиту (X9, X14) и тактику (X18, X19). Врезультате такого распределения статистически значимых коэффициентов соревновательная компетентность (X22) исследуемых групп отличаетсямало: во II она составляет – 40,89%; в III – 36,43%.

Анализ показателей дзюдоистов III группы веса до 46 кг и IIгруппы веса до 42 кг показал следующее. В III группе достоверно выше такие показатели: объемы соревновательной (X2, X3) и эффективной (X4, X5) техник, соревновательная эффективность защиты (X9), качественная надежность защиты стоя (X14), техничность (X16), комбинационность атакующих действия стоя (X18), показатель контратакующих действий стоя (X19),коэффициент асимметрии техники стоя (X20), метания теннисного мяча в цель (X23), прыжок в длину с места (X28), подтягивания в висе (X29), простая двигательная реакция (X32), тест Малиновского С.В. (X35), оценка выполнения 10-ти бросков через спину (X37), коэффициент специальной выносливости (X38). Во II группе выше такие показатели: объем проигранной техники (X6, X7),

интервал успешной атаки (X11), качественная надежность атак стоя (X12) и защиты лежа (X15), общая выносливость (X31), реакция на движущийся объект (X34), время выполнения 10-ти бросков через спину (X36). Анализ соревновательных коэффициентов показывает, что у спортсменов III группы шире арсенал технических действий (X2 - X5, X20), выше показатели защиты (X9, X14) и тактики (X18, X19), лучше соотношение выигранных и проигранных приемов (X16). У спортсменов II группы меньше проигранных технических действий (X6, X7), лучше атака (X11, X12) и защита в борьбе лежа (X15). То есть, однозначного преимущества какой-либо из групп в показателях соревновательной деятельности нет. Соответственно нет существенной разницы в соревновательной компетентности (X22): в III группе она составляет 36,43%; а во II - 33,41%. По результатам тестирования лучше оказались спортсмены III группы, чтовполне закономерно.

Сравнение двух групп одной весовой категории до 46 кг выявило различия в ОСТС (X2), ОСТЛ (X3), ОЭТС (X4), СЭА (X8), СЭЗ (X9), Иа (X10), Иуа (X11), КНАС (X12), КНАЛ (X13), КНЗС (X14), техничности (X16), КАДС (X18), КАТС (X20), соревновательной компетентности (X22), метаниях теннисного (X23) и толканиях набивного (X24) мяча, отжиманиях в упоре лежа в течение 15-ти секунд (X26), прыжке в длину с места (X28), подтягиваниях в висе (X29), приседаниях с партнером (X30), общей выносливости (X31), скорости сложной двигательной реакции (X33), тесте Малиновского С.В. (X35), оценке выполнения 10-ти бросков через спину (X37), коэффициенте специальной выносливости (X38). У спортсменов II группы преимущество в атаке (X4, X8, X10 - X12), соревновательной компетентности (X22). У спортсменов III группы – в арсеналетехники (X2, X3, X20), защите (X9, X14), атаке лежа (X13), соотношении выигранных и проигранных приемов (X16), тактике (X18)[3-5]. По результатам тестирования спортсмены III группы уступили спортсменам II группы только в прыжке в длину (X28) и беговом тесте на общую выносливость (X31). Это вполне оправданно, поскольку многие дзюдоисты в 15 - 17 лет выполняют норматив кандидата в мастера спорта или мастера спорта. Тем не менее, несмотря на более высокий уровень подготовленности, в атаке они оказались менее активны, что и повлияло на величину соревновательной компетентности (X22): во II группе она составляет 41,02%; в III - 36,43%.

В весовой категории до 50 кг между группами различия оказались в 23 показателях: объемах соревновательной (X2, X3), эффективной (X4, X5) и проигранной (X6) техник, интервалах атаки (X10, X11), качественной надежности атак лежа (X13) и защиты стоя (X14) и лежа (X15), техничности (X16), показателе преследований в борьбе лежа (X17), результате показанной эффективности (X21), соревновательной компетентности (X22), метаниях теннисного мяча в цель (X23), беге на 60 м (X25), отжиманиях в упоре лежа в течение 15-ти секунд (X26), подтягиваниях в висе (X29), приседаниях с партнером (X30), общей выносливости (X31), скорости реакции на движущийся объект (X34), времени выполнения 10-ти бросков через спину (X36),коэффициенте специальной выносливости (X38). Спортсмены IIгруппы оказались лучше по двум показателям соревновательной деятельности (X6, X17) и по двум –подготовленности (X23, X31). Такое подавляющее преимущество дзюдоистов IIIгруппы не случайно. Поскольку в отличие от двух предыдущих возрастных групп это уже сформировавшиеся спортсмены, достигшие определенных высот в дзюдо. Поэтому соревновательная компетентность (X22) у них составляет 49,54%; в другой группе - 27,57 %.

В весовой категории до 55 кг группы достоверно отличаются по следующим показателям: ОЭТЛ (X5), ОПТЛ (X7), КНАЛ (X13), техничности (X16), ППБЛ (X17), КАДС (X18), ПКАДС (X19), КАТС (X20), РПЭ (X21), соревновательной компетентности (X22), сгибаниям туловища до прямого седа в течение 20-ти секунд (X27), подтягиваниям в висе (X29), приседаниям с партнером (X30), скорости сложной двигательной реакции (X33), РДО (X34), оценке выполнения 10-ти бросков через спину (X37). Из перечисленных показателей только в двух лучше спортсмены II группы: X20, X27. Причина столь существенной разницы в уровне тренированности. Спортсмены II группы занимаются три раза в неделю. В то время как спортсмены III группы занимаются шесть,а то и двенадцать раз в неделю со сборной командой Кыргызстана. К тому же, возраст 15 - 17 лет характеризуется интенсивным ростом физических возможностей [6].Соревновательная компетентность (X22) в III группе достоверно выше, чем во II: 43,78% и 35,22% соответственно.

В весовой категории до 60 кг различия между группами присутствуют по следующим показателям: объемам соревновательной (X2, X3), эффективной (X4, X5) и проигранной (X6, X7) техник, соревновательной эффективности защиты (X9), интервалам атаки (X10, X11), качественной надежности атак лежа (X13) и защиты стоя (X14) и лежа (X15), показателю преследований в борьбе лежа (X17), показателю контратакующих действий в стойке (X19), коэффициенту асимметрии техники стоя (X20), результату показанной эффективности (X21), соревновательной компетентности (X22), сгибаниям туловища до прямого седа втечение 20-ти секунд (X27), подтягиваниям в висе на перекладине (X29), приседаниям с партнером собственного веса (X30), скорости двигательнойреакции (X33, X34). Во II группе меньше проигранных приемов (X6, X7) и выше коэффициенты атаки (X10, X11, X13). В III группе преимущество в разнообразии технических действий (X2 - X5, X20), защите (X9, X14, X15), показателях

тактики (X17, X19), общей эффективности в поединках (X21). Соревновательный опыт и надежная защита у спортсменов III группы даже при более низкой частоте атак и незначительном преимуществе в подготовленности (в 5 показателях из 16) позволили продемонстрировать более высокую соревновательную компетентность (X22) – 42,19% против 38,47% во II группе.

Вывод. Подводя итог сравнению испытуемых II и III групп, можно отметить, что показатели подготовленности у спортсменов III группы выше, чем у II, кроме X31, X32, X36. Если за основу брать большинство весовых категорий (не менее четырёх), то преимущество у спортсменов II группы в объёме проигранной техники стоя (X6), интервале успешной атаки (X11), общей выносливости (X31); у спортсменов III группы - в объёмах соревновательной (X2, X3) и эффективной (X4, X5) техник, соревновательной эффективности защиты (X9), качественной надёжности защиты стоя (X14), техничности (X16), комбинационности атакующих действий стоя (X18), показателе контратакующих действий стоя (X19), коэффициенте асимметрии техники стоя (X20), результате показанной эффективности (X21), соревновательной компетентности (X22), количестве подтягиваний в висе (X29) и приседаний с партнёром собственного веса (X30), скорости сложной двигательной реакции (X33), тесте Малиновского С.В. (X35), оценке выполнения 10-ти бросков через спину (X37). Подавляющее преимущество в показателях соревновательной деятельности отразилось на величине соревновательной компетентности (X22) - она достоверно выше в четырех весовых категориях и составляет: 36,43%; 49,54%; 43,78%; 42,19%. У дзюдоистов II группы соревновательная компетентность (X22) выше только в категории до 46 кг и составляет 41,02%. Это вполне закономерно. Возрастиспытуемых II группы – 13 - 14 лет, что примерно соответствует первой половине этапа углубленной специализации. Тренируются они три раза в неделю. Возрастиспытуемых III группы – 15 - 17 лет, что соответствует второй половине этапа углубленной специализации и началу этапа спортивного совершенствования [7]. По сути, это уже сформировавшиеся спортсмены, многие из которых имеют звание кандидата в мастера спорта КР. Некоторые из них участвуют в соревнованиях мужчин. Поэтому разница очевидна.

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Ultrasound-Guided Central Venous Catheterization. Study Guide

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Abstract- Central venous catheterization consists of the insertion of a catheter into the central vascular space for diagnostic or therapeutic purposes. Current evidence recommends the use of ultrasound guidance for the insertion of central venous catheters (CVCs), enabling real-time visualization of the procedure while increasing safety and probability of success. It also reduces intervention time and complications. This literature review article presents the advantages, contraindications, procedure technique and most frequent complications of Doppler ultrasound-guided central venous catheterization.

MeSH: central venous catheters. ultrasonography, interventional.

GJMR-K Classification: NLMC Code: WG 141.5.C2

ULTRASOUNDGUIDEDCENTRALVENOUSCATHETERIZATIONSTUDYGUIDE

Strictly as per the compliance and regulations of:

Ultrasound-Guided Central Venous Catheterization. Study Guide

Adriana Almario [α], Michel Hernández [σ] & William Prada [ρ]

Abstract- **Central venous catheterization consists of the insertion of a catheter into the central vascular space for diagnostic or therapeutic purposes. Current evidence recommends the use of ultrasound guidance for the insertion of central venous catheters (CVCs), enabling real-time visualization of the procedure while increasing safety and probability of success. It also reduces intervention time and complications. This literature review article presents the advantages, contraindications, procedure technique and most frequent complications of Doppler ultrasound-guided central venous catheterization.**

MeSH: central venous catheters. ultrasonography, interventional.

I. Introduction

Central venous catheterization is a frequent procedure in medical practice performed in image-guided interventionism services, emergency services, surgical, intensive care units, and hemodialysis units, among others. Venous catheterization is the technique whereby a catheter is inserted into the central vascular space for diagnostic or therapeutic purposes (1–4). The international recommendation today is the insertion of central venous catheters (CVCs) using Doppler ultrasound to guide the procedure (5–12). In addition to the advantages for elective procedures, the use of Doppler ultrasound-guided CVC implantation in cases of difficult venous access is widely known and recommended (13–17).

CVCs are placed in large venous vessels such as the internal jugular vein, subclavian vein, common femoral vein or superficial femoral vein, vena cava or suprahepatic veins, and for each of these structures the advantages of ultrasound guidance have been extensively studied (18,19). Likewise, peripherally inserted central catheters (PICCs) can be selected when there are no prothrombotic states present, since the latter increase thrombosis cases caused by the length and the vein-catheter relationship, increasing venous stasis (1,3).

II. Indications

The most frequent indications include hemodynamic monitoring (measurement of central venous pressure or pulmonary artery wedge pressure), administration of medications or parenteral nutrition, impossibility of peripheral venous access, hemodialysis, plasmapheresis, potassium replacement at large doses and implantation of cardiac pacemakers (1,20–23).

Contraindications (absolute and relative).

- Absolute: infection at the puncture site, venous thrombosis.
- Relative: Coagulopathy, poor patient cooperation (24,25).

III. Types of Catheters

- Non-tunnelled high-flow central venous catheter
- Tunnelled high-flow central venous catheter
- Low-flow central venous catheter
- Implanted Central Venous Access Port (with a reservoir)
- Antibiotic- or antiseptic-impregnated catheter
- Swan-Ganz catheter
- Peripherally inserted central catheter (PICC)

IV. Technical Considerations Prior to Conducting the Process

Knowledge of the technical aspects of ultrasound and the characteristics of the equipment optimizes assessment prior to conducting the procedure as well as its correct display (26). High-frequency B-mode ultrasound serves to evaluate structures displayed on a gray-scale image, in real time and in different anatomical planes. Venous vessels are visualized as anechoic structures with echogenic thin and regular walls, most of the time exhibiting a greater diameter than their accompanying arteries. In some locations, with excellent image quality, it is possible to identify the venous valves which should be avoided when inserting catheters (27,28). Depending on transducer orientation, the venous vessels and the catheter are identified as tubular structures (in a longitudinal plane of the transducer with the vessel) or oval structures (if the transducer is placed transverse or axial to the axis of the vessel) (Image 1) (6). However, in some special cases, such as the catheterization of the internal jugular vein, it is possible to perform oblique orientations, where the vessel is projected in the axial plane and the needle in the longitudinal plane (scheme 1) (29).

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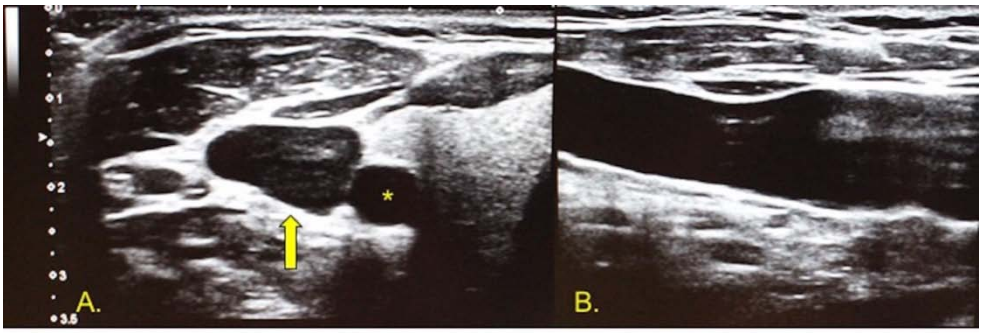
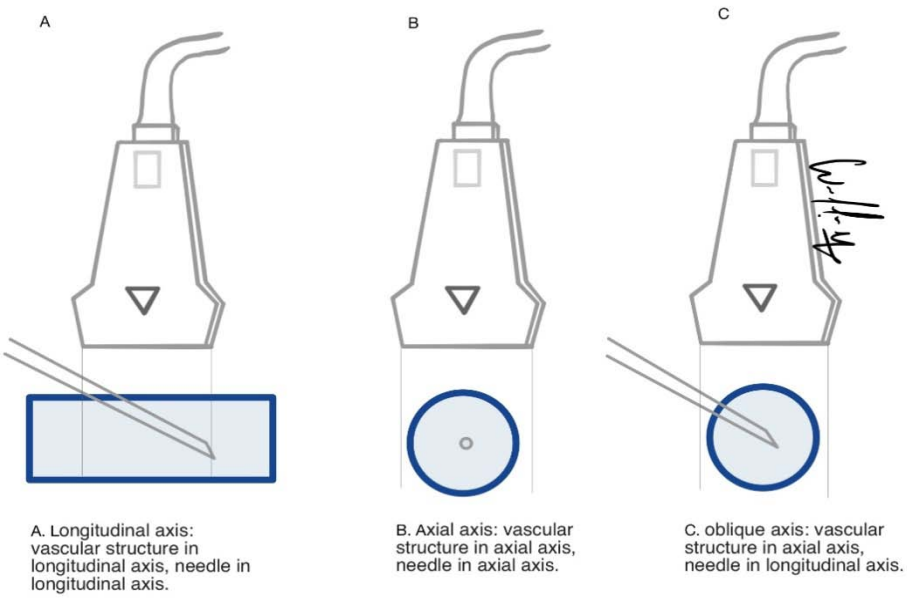


Image 1: Transverse (A) and longitudinal (B) image of the internal jugular vein (arrow). The common carotid artery (*) has a medial location with respect to this.



Scheme by William Prada.

Scheme 1: Technical considerations in the axial and longitudinal axis of the transducer and vascular structure.

Under normal conditions the venous vessels collapse with gentle compression with the transducer and, increase their caliber with the Valsalva maneuvers (Image 2). Knowledge of normal vascular anatomy, anatomical variants and possible pathological conditions that may hinder the correct characterization of venous vessels is essential (30,31). In most cases, the internal jugular vein is located anterolateral to the common carotid artery (image 3) presenting a diameter that varies between 5 and 11.5 mm. The right vein diameter is relatively greater than the left, in up to 65% of cases (32), and the right is also generally preferred as the first option for catheter placement.

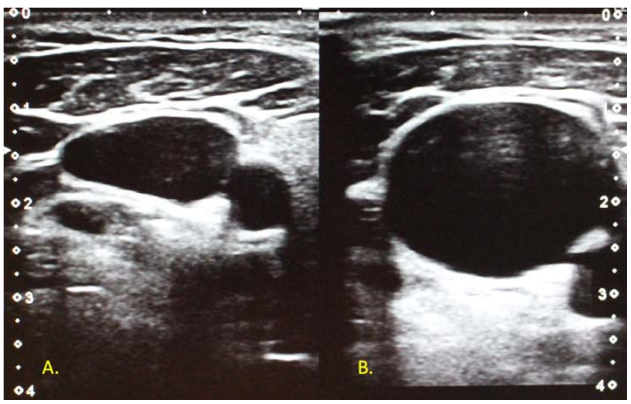


Image 2: transverse image of the internal jugular vein at rest (A), during the Valsalva maneuver (B), there is an increase in caliber.

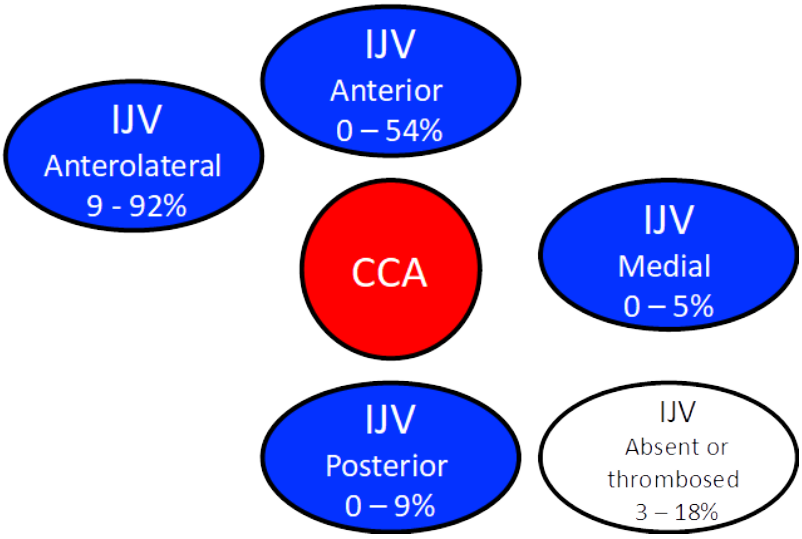


Image 3: Legend: Locations and percentages of the Internal Jugular Vein (IJV) with respect to the Common Carotid Artery (CCA)

The common femoral vein is made up of its tributaries: the deep femoral vein and the femoral vein (previously known as the superficial femoral vein), is located approximately 9 cm from the inguinal ligament and medial to the common femoral artery (Image 4). Proximally, the femoral vein runs medially to the artery, but, distally, it crosses over it and is located laterally (33). In some percentages and especially in the pediatric population, the femoral artery may adopt an anterior location to the vein (34).

The subclavian vein is the continuation of the axillary vein, delimited at the superior edge of the first rib (where the axillary vein receives its tributary, the cephalic vein) to the sternoclavicular joint at its junction with the internal jugular vein, forming the jugulo-subclavian confluent. It presents an arched path towards the cephalic region, its anterior wall is related to the posterior facet of the clavicle and its posterior wall is related to the subclavian artery, anterior scalene muscle, first rib and pleura (27).

Examination with color Doppler and pulsed-wave Doppler facilitates differentiation between arterial and venous structures, as well as the assessment of their patency. The veins have spontaneous and phasic flow (which vary with the respiratory and cardiac cycle) (27) (Image 4).

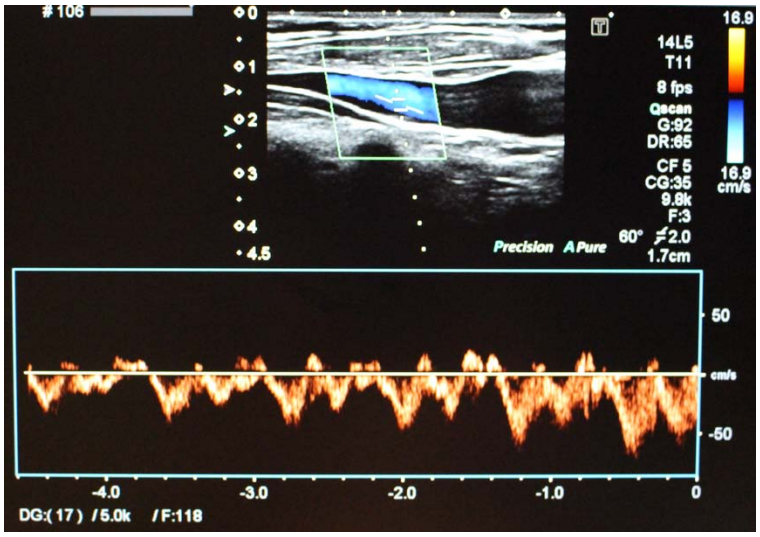


Image 4: Color and Pulsed Doppler of the internal jugular vein showing permeability and normal phasic pattern.

Vein selection for catheterization depends on the patient's clinical conditions, the knowledge of the individual risks of puncture sites and the technical limitations or facilities (Table 1).

Table 1: Main Aspects to Consider When Selecting Specific Veins for Catheterization.

VEIN	ADVANTAGES	DISADVANTAGES
Internal Jugular	Easier ultrasound guide. External compression is possible. Lower risk of mechanical complications. Lower risk of thrombosis or stenosis.	Patient discomfort.
Subclavian	Patient confort. Lower risk of thrombosis or stenosis.	More difficult ultrasound guide. External compression is difficult. Increased risk of pneumothorax.
Femoral	Easier ultrasound guidance. External compression is possible.	Patient discomfort. High risk of thrombosis and increased risk of infection.

a) Seldinger Technique, Modified Seldinger and Process Description

The Seldinger technique, described by Radiologist Sven Ivar Seldinger in 1953, is used for percutaneous vascular catheterization with needle puncture and blood return (35-37). The advent of ultrasound and its use as a guide for procedures prompted a modification of the Seldinger technique, resulting its use in many interventional radiology procedures (biliary and urinary tract intervention, collection drainage, etc.).

Once the vessel has been channeled, a guide is inserted through the needle, the needle is withdrawn and a catheter is inserted through the guide, after path dilation. Central venous catheterization requires a linear transducer with a 10 MHz frequency or more, ideally narrow band for better maneuverability. Before starting the procedure, it is necessary to have all the requisite supplies, check the status of the catheter, permeabilize it with saline solution and keep in mind the length to be introduced for proper location of its distal end.

The skin must be prepared using an aseptic and antiseptic technique, setting up a sterile field, and the transducer must be covered with a sterile drape. Sterile gel should be used between the transducer cover and the patient's skin, and non-sterile gel between the cover and the transducer, facilitating the transmission of the ultrasound beam. The transducer shall be located according to the anatomical landmarks mentioned below and the vessel insonated in transverse and longitudinal planes. Local anesthetic is injected into soft tissues using ultrasound guidance with two objectives: to avoid intravascular injection and to verify the catheter's access route. Subsequently, the vessel is located in the center of the screen of the equipment obtaining a longitudinal axis, taking into account that catheterization in the longitudinal axis avoids accidental arterial puncture (7,38).

The puncture should be done with a Seldinger needle, with the bevel facing up and ideally at an angle of 45° to the skin. The needle is identified as a linear echogenic structure, which projects an acoustic shadow, and its movement ("ballotment" technique) displaces the adjacent tissues, enabling its location (6). The needle is visualized continuously, entering through the anterior wall of the vessel and aspiration is performed with a syringe attached to it. Obtaining blood confirms its correct location and patency. The insertion of the guide should be visualized in the longitudinal axis of the vessel, demonstrating correct direction (39-41) (Figure 5).

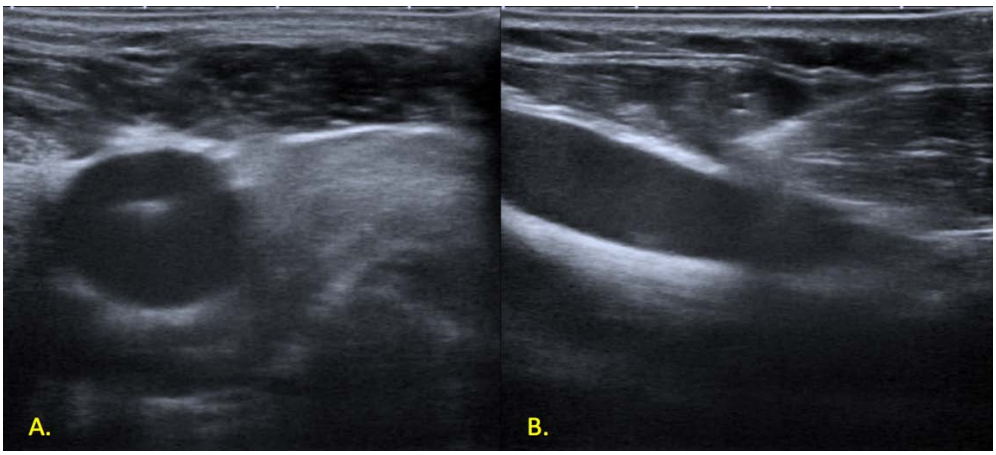


Image 5: Transverse (A) and longitudinal (B) images of the internal jugular vein, the tip of the needle is identified as a linear echogenic structure.

The use of the vessel in the axial axis should be considered in cases where the longitudinal axis is not possible, such as in jugular access in patients with a short neck. Progression of the guide, the dilator or the catheter should not put up resistance; if so, the process should not continue, since it may cause vascular dissection. The performance of these steps should be observed under ultrasound guidance (Figure 6). The ultrasound can show the cause of resistance, such as vascular stenosis, vascular thrombosis or insertion towards the opposite wall of the vessel (6). In addition, the trajectory of the guidewire toward distal should be verified and it should not move cephalad.

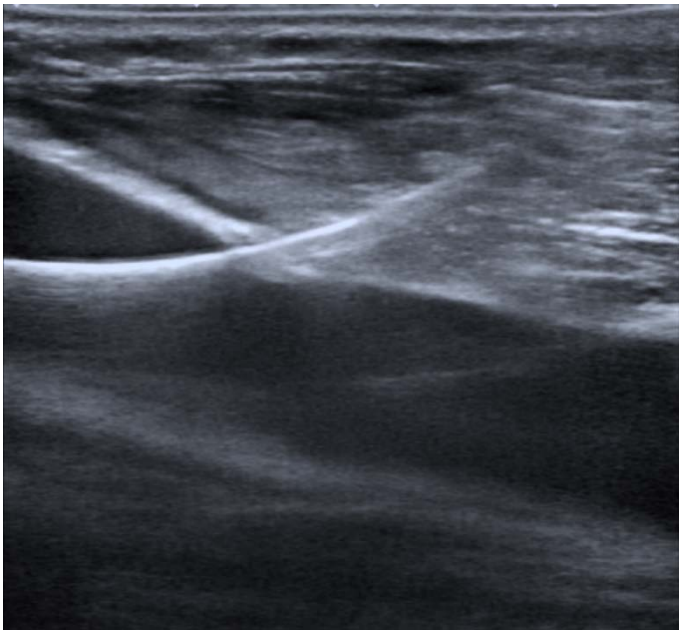


Image 6: The ultrasound allows to corroborate guide progress inside the vessel.

Once the catheter has been inserted, ultrasound can be used to identify the mildly echogenic swirling with a rapid saline flush through the catheter ports. The use of pulmonary ultrasound can be recommended as well, to verify immediate complications such as pneumothorax and focused cardiac ultrasound to verify flushing of the solution and the distal location of the catheter.

b) Anatomical Repairs and Procedure Specifications for Central Venous Catheterization

i. *Internal Jugular Vein*

The patient must be positioned supine, in the Trendelenburg position and with the head rotated to the contra lateral side by 45° (Image 7). The transducer must be placed parallel to the clavicle in the space formed between the sternal and clavicular heads of the sternocleidomastoid muscle (Sedillot's triangle) (3,6). This way, the internal jugular vein, carotid artery and sternocleidomastoid muscle are identified (scheme 2b).

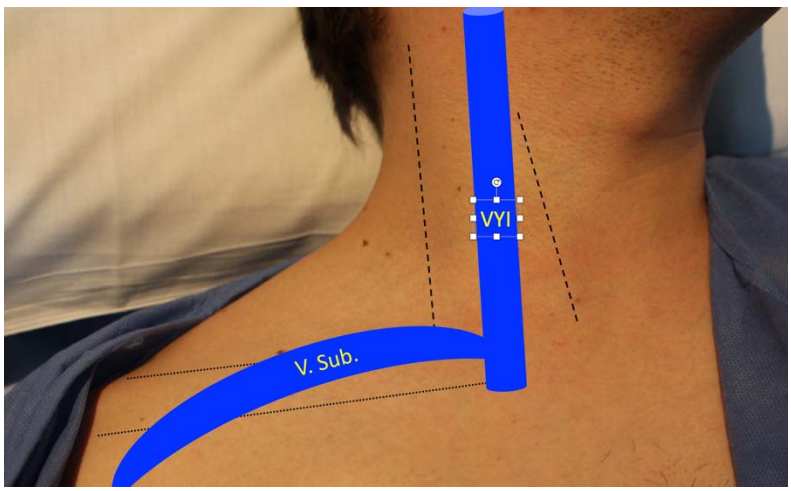
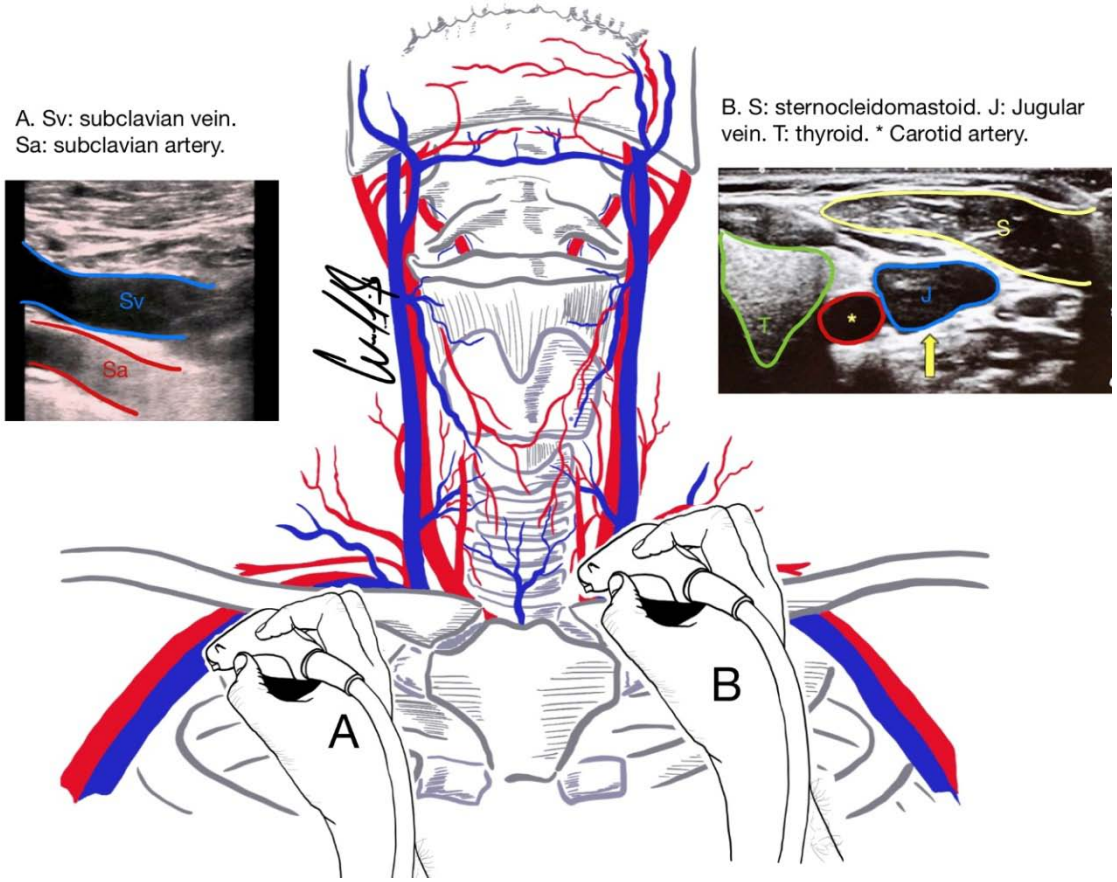


Image 7: Relationships of the internal jugular vein (IJV) with the sternocleidomastoid muscle (dashed line) and of the subclavian vein with the clavicle (dotted line).

ii. *Subclavian Vein*

The patient should be positioned supine, in the Trendelenburg position with the head rotated to the contra lateral side. A supraclavicular or infraclavicular approach can be performed (42). In the supraclavicular approach, the transducer is positioned parallel (or slightly oblique) to the medial clavicle, above it, directing the transducer beam caudally, in order to identify the jugulo-subclavian confluent (6,27). In the infraclavicular approach, the transducer is positioned parallel to the clavicle, under it, at its junction of the external third and the middle third (scheme 2a). The puncture must be delivered by directing the needle towards the sternal notch and horizontally, with respect to the chest wall. (42.43). The subclavian artery and the lung are identified below the vein, thus avoiding accidental puncture.

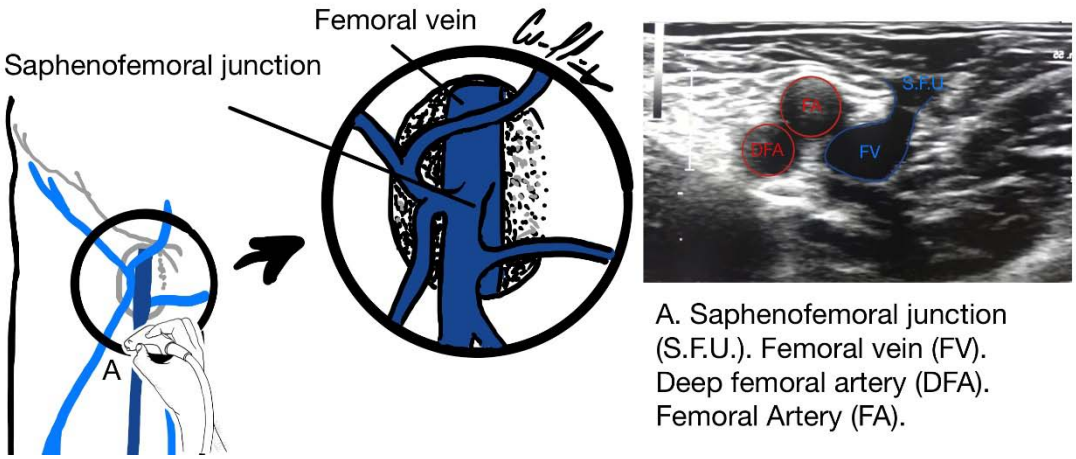


Scheme by William Prada.

Scheme 2: Patient position to place the transducer in jugular and subclavian access with anatomical relationships of interest.

iii. *Femoral Vein*

The patient should be positioned supine, in reverse Trendelenburg position (semifowler), with the hip in external rotation. The transducer should be placed longitudinally, in the medial half of an imaginary line that joins the anterior superior iliac spine and the pubic symphysis (Inguinal ligament pathway), identifying the femoral vein medial to the artery (scheme 3). The puncture should be performed below the inguinal ligament, since it facilitates control of bleeding and avoids accidental puncture of intra-abdominal structures. However, the more distal, the greater the risk of arterial puncture (42).



Scheme by William Prada.

Scheme 3: Anatomical relationships of the femoral vein on the axial axis.

V. Location of the Distal end of Catheter

With the exception of catheters for measurement of pulmonary artery pressure, it is recommended that the end of the catheter be located in the lower third of the superior vena cava (SVC) or the caval atrial junction and choosing a position parallel to the longitudinal axis of the vessel. The most widely used method to check the location of the end of the catheter is chest radiography, ensuring the location of the catheter in the extrapericardial SVC. For hemodialysis catheters, localization in the upper third of the right atrium is recommended, considering it offers specific advantages (better flow rates, reduced thrombus formation and stenosis venous) and minimal complications (44,45). The formulas established by Czepizak et al. in adult patients report an efficacy of 95% for the placement of the catheter in the superior vena cava for punctures in the internal jugular and subclavian veins (Table 2).

Table 2: Central Venous Catheter Insertion Length.

Insertion Site	Formula
Right Subclavian Vein	(Height/10) - 2 cm.
Left Subclavian Vein	(Height/10) + 2 cm.
Right Internal Jugular Vein	Height/10
Left Internal Jugular Vein	(Height/10) + 4 cm.

The optimal positioning of the distal end of femoral central venous catheters has not been extensively studied. It is recommended in the inferior vena cava below the arrival of the renal veins for administration or extraction of fluids, but not for measurement of central venous pressure (35).

VI. Complications

Up to 15% of CVCs present complications, which can be classified into mechanical, infectious and thrombotic, and in turn, into acute or chronic depending on the onset. The most frequent are those related to mechanical complications that occur between 5% and 19%, thrombotic complications between 2% and 26%, and infectious between 2% and 6% (5,42,46) (Table 3).

Table 3: Frequency of Mechanical Complications Depending on Insertion Site.

	FRECUENCY (%)		
COMPLICATION	SUBCLAVAL VEIN	INTERNAL JUGULAR VEIN	FEMORAL VEIN
Pneumothorax	1.5-3.1	< 0.1-0.2	N/A
Hemothorax	0.4-0.6	N/A	N/A
Arterial puncture	3.1-4.9	6.3-9.4	9.0-15.0
Hematoma	1.2-2.1	< 0.1-2.2	3.8-4.4

Taken from (42,47,48).

Pneumothorax is most often associated with catheterization of the subclavian vein, especially with the infraclavicular approach and less frequently with the catheterization of the internal jugular vein (49,50). Patients with pneumothorax who require pleural drainage present dyspnoea, tachypnea, coughing and/or desaturation. When this is suspected, radiographic and ultrasound monitoring should be performed (35). Hemothorax can be caused by arterial puncture or be one of the presentations of vascular perforation. It is one of the most feared complications, which occurs in 0.25% of cases and more frequently in left access, possibly due to the acute angle formed between the guide or the catheter and the wall of the SVC.

Due to the proximity of the internal jugular vein to the common carotid artery, arterial puncture is a frequent complication, which can be managed with extrinsic compression. Complications secondary to arterial puncture such as hematomas, pseudoaneurysms with or without neural compression, arterial thrombosis or dissection, cerebrovascular disease, arteriovenous fistulas, hemothorax or hemomediastinum have occurred.

Venous air embolism has an incidence of 0.8% and it can occur with the insertion, extraction or exchange of a CVC (44). It can be identified by direct observation of air bubbles in the catheter or sudden desaturation and may be reduced with the patient in Trendelenburg position (35). Benign and–to a lesser extent–malignant cardiac arrhythmias have been reported, caused by the guide or the catheter in the atrium or ventricle. If persistent, they require pharmacological or electrical intervention, and repositioning. Malposition or kinking of the device is associated with local vascular complications (phlebitis, perforation, thrombosis or occlusion), which can be suspected during catheterization with the absence of venous return and can be detected real time on fluoroscopy (50).

Puncture of the left subclavian vein is rarely associated with injury to the thoracic duct (50). Retroperitoneal hematoma is one of the most fatal complications in femoral vein catheterization, which occurs in 1.3% of patients without the use of ultrasound guidance (50).

Catheter-associated vascular infection has a significant effect on morbidity, mortality and health costs. Risk factors include poor insertion technique, emergency placement and long-term use of the catheter (49,50). Given its proximity to the perineal area, femoral vein catheterization is the one that is most associated with infectious complications, while subclavian catheterization is the least (8,49). Nevertheless, Timsit et al. published an analysis in 2013 of two clinical trials involving 2,128 patients, showing no differences in the rate of infection or colonization in the jugular and femoral catheters (P=0.34), presenting infection in 1 versus 1.1 per 1,000 catheters, respectively (50).

VII. Conclusions

The use of Doppler ultrasound guidance for central venous catheterization is becoming increasingly popular in medical practice. The known advantages widely recommend its use to the point that, if not performed, it is considered bad clinical practice. Knowledge of venous anatomy and its features, the procedure technique and the physical properties of ultrasound are very useful to conduct a successful procedure. It is important to have experience in all the anatomical routes of ultrasound-guided venous catheterization and with the different techniques in order to deliver better results when facing vascular access.

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Memberships

Fellows/Associates of Medical Research Council

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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.

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Acknowledgments

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- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
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- First character must be three lines drop-capped.
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- 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.

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

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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.

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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.

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

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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.

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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.

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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.

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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).

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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.

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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:

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The discussion section:

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

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

General style:

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

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

Mistakes to avoid:

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

Title page:

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

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

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

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

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

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

Approach:

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

Introduction:

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

The following approach can create a valuable beginning:

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

Approach:

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

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

Procedures (methods and materials):

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

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

Materials:

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

Methods:

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

Approach:

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

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

What to keep away from:

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

Results:

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

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

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

Content:

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

What to stay away from:

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

Approach:

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

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

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

Figures and tables:

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

Discussion:

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

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

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

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

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

Approach:

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

Describe generally acknowledged facts and main beliefs in present tense.

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

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