Prevalence of post-covid complications in a follow-up survey of participants of two Homoeopathy-based RCTs on moderate and severe cases of COVID-19: A cross-sectional study

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Abstract

Background: Coronavirus disease 2019 (COVID-19) was declared a global pandemic by WHO on 11th March 2020. Witnessing the pattern of relapse of cases, varying severity of cases and persistence of symptoms through different waves of pandemic has emerged as the reason for the studies targeting post-covid status of individuals.

Objective: The objective of this survey was to assess the long-term effectiveness of homoeopathic medicines when used as an adjunct therapy along with the conventional therapy during covid infection in oxygen-dependent, moderate and severe patients.

Methods: The survey was carried out from 1st April 2022 to 29 May 2022 via telephonic conversation among 219 participants who were discharged from AIIMS, Jhajjar, Haryana and St. George Hospital, Mumbai, India and had participated in two different placebo-controlled, randomised trials held at these two hospitals where individualised homoeopathic medicines were given to the experimental groups in addition to the conventional treatment. The post-COVID-19 Functional Status (PCFS) Scale was employed to evaluate the functional status of the surviving survey participants and to compare the status between the add-on Homoeopathy (AoH) group and the add-on placebo (AoP) group.

Results: The mean score of PCFS Scale between the groups were compared using the chi-square test, which was presumed to be statistically significant at $P<0.05$. In total, 93 participants of AoH group showed more functional ability with mean difference of 0.83±1.47 (mean ± SD), as opposed to 1.33±1.63 (mean ± SD) among the AoP group participants (P=.04). Percentage of participants who developed post-COVID diabetes mellitus or hypertension, or shortness of breath on exertion and was found to be 17.20%, 8.60% and 6.45%, respectively in the AoH group, as compared to 17.57%, 9.68% and 10.81%, respectively in the AoP group. No incidence of post covid anxiety, pneumonia and chronic/acute kidney disease was reported in the AoH group while it was 1.35%, 1.35% and 4.05% respectively in the AoP group. The ability to perform daily chores was observed to be in 57% of the participants of AoH group, as against 43% of those in the AoP group.

Conclusions: Homoeopathy, when given as an add-on therapy in COVID-19, helps in faster recovery from acute infections such as COVID19, with a higher proportion of participants being able to perform daily chores, along with an improvement in their general weakness, even after the medicine was discontinued. This proved the long term effectiveness of homoeopathic treatment when used as an adjunct therapy along with the conventional therapy in the oxygen-dependent, moderate or severe patients of COVID-19. Clinical Trial: As it was a survey, trial registration is not mandatory.

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Introduction

Coronavirus disease 2019 (COVID-19) was declared a global pandemic by WHO on 11th March 2020. Several studies have since been undertaken to determine the course of the disease, sequelae of the disease and complications of the standard treatment. Witnessing the pattern of relapse of cases, varying severity of cases and persistence of symptoms through different waves of the pandemic has emerged as the reasons for the studies targeting post-covid status of individuals.

Medium and long-term problems are being experienced by the COVID-19 survivors even after discharge, which are reported worldwide. A study which took telephonic follow-ups of COVID-19 survivors after around 110 days of discharge from Intensive Care Unit (ICU) listed the few commonest symptoms experienced by them. Fatigue (58%) was the most frequently reported symptom to be followed by dyspnoea (50%), sleep disorders (33.3%), loss of memory (20.8%), and poor concentration (16.7%).[i] In the same study, 29.17% patients admitted in ICU died within 3 months of hospital admission. However, Health-related quality of life (HRQoL) was quite satisfactory amongst the population who belonged to the working sector and joined their work post-discharge. Stephen J. Halpin et al in their telephonic cross-sectional study also reported fatigue as the commonest persisting symptom in about 72% of COVID survivors even after 4-8 weeks of discharge from ICU. Dyspnoea (65.6%) and psychological stress (46.9%) were reported as the next most common symptoms.[ii] This study also encountered a significant drop in EuroQol 5 Dimension (EQ-5D) score in about 68.8% ICU admitted patients post-discharge, which reflects the impact of the illness on quality of life and health burden to the economy. In another study 31.25% patients belonging to the moderate to severe category of COVID-19 showed persistence of at least one symptom even after about 169 days from onset of the disease.[iii]

A study amongst healthcare workers in Sweden, reported that some symptoms persisted even after 8 months amongst 15% of RTPCR-positive subjects and also amongst 3% of RTPCR-negative subjects. They showed the presence of at least one symptom, viz., anosmia, fatigue, ageusia, and dyspnoea. This study significantly points out the presence of at least one symptom amongst the low-risk group of subjects who reported mild COVID-19. The same study also infers about the long-term effects on work, social and home life of the COVID-19 survivors. Thus, the presence of more complex symptoms is anticipated amongst moderate to severe COVID-19 survivors with long-term disruption in QoL.[iv]

Prior research has identified various potential long-term complications associated with COVID-19 infection, encompassing conditions such as lung fibrosis, venous thromboembolism (VTE), arterial thromboses, cardiac thrombosis and inflammation, stroke, cognitive impairment, dermatological issues, and mood disorders.[v] Numerous long-term pulmonary complications have been documented post COVID-19 infection. These encompass dyspnoea, reliance on ventilators or oxygen, abnormalities in pulmonary function tests (PFTs), and the development of fibrotic lung conditions. Among these, dyspnea emerges as the most frequently reported symptom, persisting in 22.9%–53% of patients approximately two months after the onset of symptoms.[vi][vii][viii] In the INSPIRATION-S trial, ICU patients diagnosed with COVID-19 were enrolled and randomly assigned to either receive a daily dose of 20 mg of atorvastatin or a placebo. Upon evaluation for the primary composite endpoint, encompassing all-cause mortality at 30 days, occurrences of venous or arterial thrombosis, or utilization of extracorporeal membrane oxygenation (ECMO), atorvastatin did not demonstrate any advantage over the placebo. [ix] In a study involving 402 patients who were discharged from the hospital after COVID-19, with a follow-up period of one month, Mazza et al. documented rates of post-traumatic stress disorder (PTSD) at 28%, depression at 31%, anxiety at 42%, and insomnia at 40%.[x]

The post-COVID-19 Functional Status (PCFS) Scale is a well validated scale which was used to assess associations between functional status and all domains of Health-related quality of life (HRQoL). This scale can be utilized to discriminate between the subjects related to the domains with reduced HRQoL and impairment in daily activities.[xi] In this study, we have used the PCFS scale for a better assessment of HRQoL among the moderate to severe COVID-19 survivors. The objective of this survey was to assess the long-term therapeutic potential of homoeopathic medicines administered as an adjunct therapy, along with the conventional therapy, as a part of randomised control trials during Covid-19 infection in oxygen-dependent, moderate severe patients.[xii][xiii]

Materials and methods

Study Design

This is a cross-sectional, post-COVID, follow-up survey of the surviving participants of two homoeopathy-based randomised controlled trials (RCTs) conducted separately by the authors, at AIIMS, Jhajjar, Haryana and St. George Hospital, Mumbai from October – December 2020, from January- June 2021, respectively. These periods happened to report peaks in the incidence of COVID 19 infection waves in India.

Study setting

The survey was carried out via telephonic conversation with the participants by

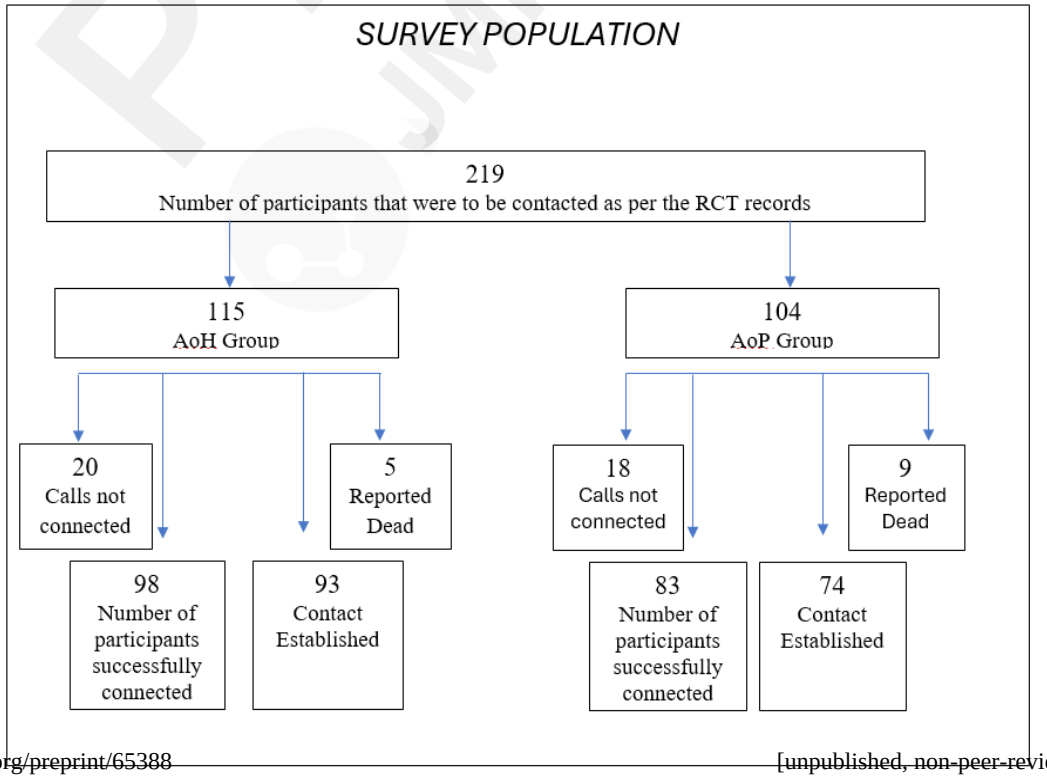
the investigators from Autonomous Research Institutes (Blinded for the review process).

Recruitment of study participants and survey process

Participants of the two RCTs who achieved the endpoint of oxygen withdrawal and/or who were discharged alive from either of the two hospitals during homoeopathic RCTs and those who completed 28 days of follow-up (maximum days of administration of intervention) were included in the survey. Participants who expired during the RCTs, those who dropped out from the RCTs; and those who couldn't be connected via telephone were excluded from the study (Figure 1).

Data from both the Homoeopathic RCTs was retrieved. There were two groups in these RCTs. The participants were randomly allocated to receive either add-on homoeopathy (AoH) or add-on placebo (AoP) along with standard care for Covid-19. A total of 219 patients from both the studies were thus targeted for detailed telephonic conversation for the survey, excluding 11 dropouts and 35 casualties. Out of 219, only 181 patients could be telephonically connected. The remaining 38 calls patients could not be connected through the numbers provided by them in their medical records. Out of 181 patients, 14 were reported to have expired by their family members. As a result, 167 patients were included in the study. Out of 167, 93 patients belonged to the experimental group at the time of RCT, that is, they received both standard care and add-on homoeopathy. The remaining 74 patients belonged to the control group and received standard care treatment and placebo. A detailed account of this is shown in the Figure 1.

Figure-1: Flowchart depicting population surveyed



The respondents were telephonically contacted and their informed response was recorded only if they agreed to participate in the survey. They were informed about the survey and the purpose behind this. Anonymity of the respondents was assured over the call, following which their verbal consent was taken. No intervention was advised during this survey.

Once they agreed to participate, details about their health status were taken according to the PCFS questionnaire and the respondent was accordingly classified into Grades 0,1,2,3 and 4, based on their level of ability to do various activities/ duties on usual basis. Grade 0 signifies no functional limitations, Grade 1: negligible functional limitations, Grade 2: Slight functional limitations, Grade 3: Moderate functional limitations, and Grade 4: severe functional limitations.

To further explain these questions of the survey and/or to understand their overall health, the respondents were also asked the following questions:

1. Are you able to eat independently?
2. Are you able to walk independently?
3. Are you able to use toilet independently?
4. Are you able to manage routine hygiene daily?
5. Do you feel breathless while doing your usual activities?
6. Is there any activity at home or at work that you are not able to perform by yourself? If yes, then which one?
7. Do you think you have any symptom of pain/depression/anxiety? If yes, then specify the symptom.
8. Do you need to avoid or reduce your usual duties/ activities or spread those over time to complete?

Statistical methods

All data were entered through a coded system in the MS Office Excel Sheet (v 2019, Microsoft Redmond Campus, Redmond, Washington, United States), and thus proofed for entry errors. Data thus obtained was compiled and subjected to the statistical analysis using Statistical Package for social sciences (SPSS v 26.0, IBM). Descriptive statistics like frequencies and percentage for categorical data. Intergroup comparison (2 arms) was done using a t-test. Comparison of frequencies of categories of variables (PCFS Scale) with groups was done using the chi-square test. For all the statistical tests, $P<.05$ was considered to be statistically significant, keeping α error at 5% and β error at 20%, thus giving power to the study as 80%.

Results

Distribution of post-covid complications

Out of 93 participants contacted for the survey in the homeopathy arm, 20 (21.5%) reported of one or more post-covid complications, as opposed to 35 out of 74 (47.3%) in the control group who reported at least one condition. A demographic break-up of the reported morbidities is reflected in Table – 1.

Table – 1: Post-covid complications as reported in both groups

POST-COVID COMPLICATIONS/SYMPTOMS	*AoH Group n=93 (%)*	*AoP Group n=74 (%)*
Diabetes Mellitus	16 (17.20)	13 (17.57)
Shortness of breath/ Dyspnoea on exertion	8(8.60)	9(9.68)
Anxiety	0	1 (1.35)
Pneumonia	0	1 (1.35)
Hypertension	6 (6.45)	8 (10.81)
Chronic kidney disease/Acute kidney disease	0	3 (4.05)
Total	*20 (21.5%)*	*35 (47.3%)*

Post-Covid Functional Status Scale (PCFS)

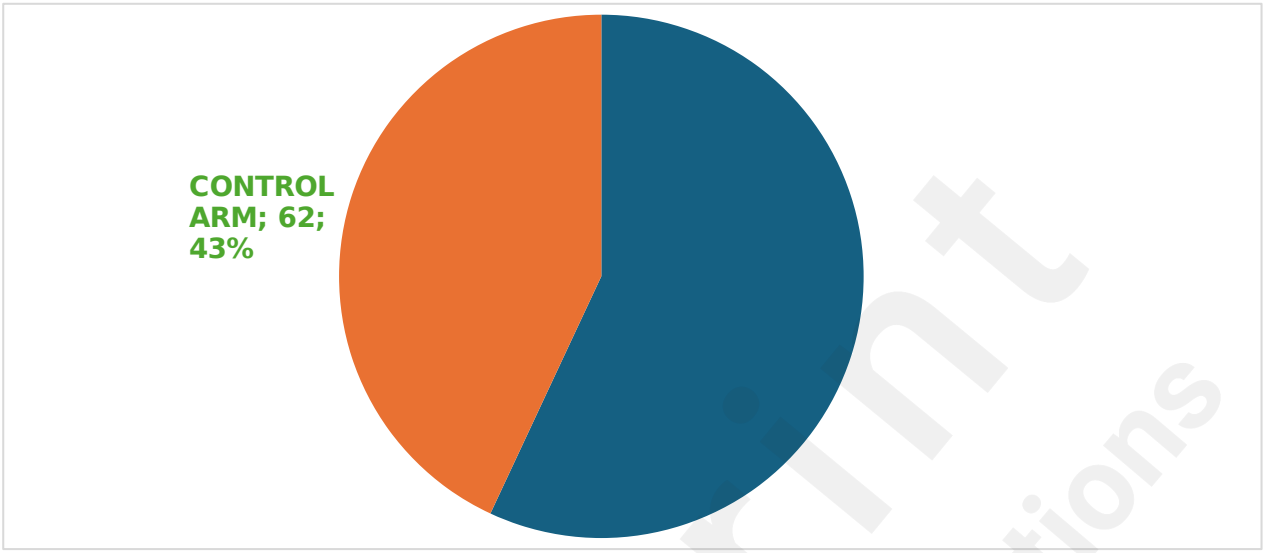
The primary outcome of the survey was to assess the functional status of the survey participants using the PCFS scale. Post Covid Functional Status Scale was used to assess the occurrence of post-covid complications among the participants. The mean PCFS score of patients taking add-on homoeopathy (AoH) was 78 (0.84 ± 0.15), while that of patients taking add-on placebo (AoP) was 99 (1.33 ± 0.18); this difference was found to be statistically significant (*P*=.04) (Table- 2).

Table - 2: Cumulative mean score of PCFS of AoH and AoP groups

Group	n	Mean ±SD	CI (95%)	*P*-Value
AoH	93	0.83±1.47	0.53-1.14	.04
AoP	74	1.33±1.63	0.95-1.71	

One of the factors of the PCFS scale, 'Frequency of ability to do daily activities' was analysed separately due to its long-term relevance. In the AoH group, it was found to be 88.2%, whereas in the AoP it was 83.8% (Figure 2).

Figure-2: Ability to do daily activities



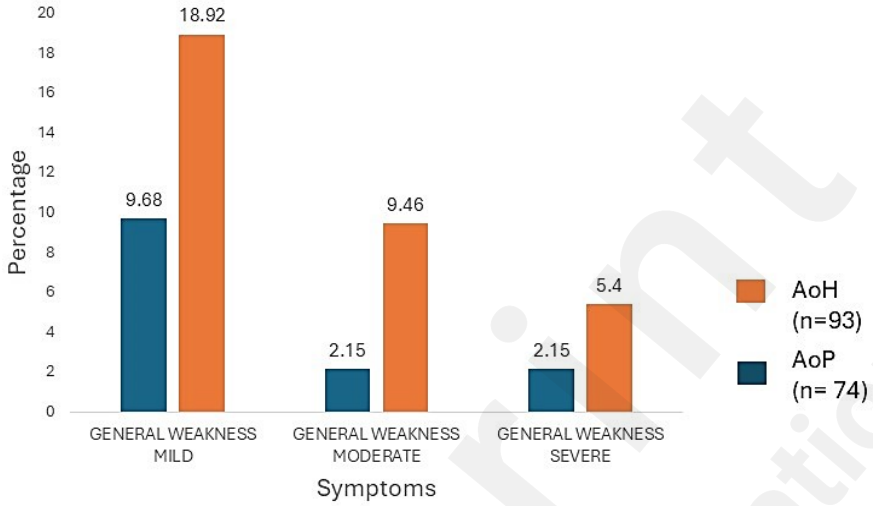
Further, the overall gradation of the post-covid symptoms among the survey respondents was seen to be on the lower side in the AoH group, with 72% reporting of no symptoms, as opposed to 52% who reported no functional limitations in the AoP group (39). The distribution as per grading of PCFS scale is shown in Table - 3.

Table 3: PCFS Scale grading

Grading in PCFS Scale	*AoH (n=93)*	*AoP (n=74)*
Grade 0	67 (72.04%)	39 (52.70%)
Grade 1	5 (5.37%)	9 (12.16%)
Grade 2	1 (1.07%)	0
Grade 3	9 (9.67%)	14 (18.91%)
Grade 4	11 (11.82%)	12 (16.2%)

Further, the commonest symptom present amongst the participants was overall weakness, which was observed to be present in about 14% in AoH group and 33.78% in the AoP group. Out of 13 respondents who reported of weakness in the AoH group, 9 reported only mild weakness, and one each reported moderate and severe weakness. In the AoP group, out of 25, 14 reported mild weakness, 7 moderate and 4 reported severe weakness (Figure 3).

Figure-3: Grading of Weakness



Discussion

Following the initial seroconversion of RT-PCR from positive to negative, and a reduced dependence of patients on oxygen among the patients receiving additional homeopathic treatment in the previous RCTs, along with the subsequent relief from all other COVID-19 symptoms during the RCT phase, this subsequent exploratory survey aimed to identify post-COVID complications in these patients and to assess the long term therapeutic effect of homoeopathic medicines in COVID-19. This exploration sought to assess the potential for enhanced *in vivo* immunity, facilitated by adjunct homeopathic therapy, to mitigate the progress of disease to further morbidities or mortalities.

Post-covid complications encountered during the survey could be inferred either as a sequel to the disease itself, due to the various treatment modalities offered during the intensive care or simply as a result of other health factors. The extent of disease, severity of disease, oxygen dependency, organ affection and various treatment protocols are some of the variables leading to different post-covid complications. A study by Garrigues E et al reported fatigue amongst 58% of the cases as a post-covid entity. He also found out that fatigue was persistent even after 100 days of the disease onset.[i]

A significant portion of COVID-19 patients are reported to develop post-COVID-19 syndrome within a week of recovery. Fatigue was the most common post-COVID symptom, followed by persistent cough, dyspnea, and other neurological and sleep disturbances.[xiv] A substantial portion of individuals who initially experienced cough, fatigue, or shortness of breath due to COVID-19 continued

to suffer from these symptoms weeks later, demonstrating that the illness can have long-lasting effects even in milder cases.[xv] One of the commonest post-covid symptoms was fatigue or weakness with almost 33% of the cases experiencing this symptom. Only about 15% in the AoH group in this study reported any kind of fatigue. 68% patient suffered from mild weakness, 2.15% patient suffered from moderate and severe weakness in the AoH group, wheareas 18.92% of the patients experienced mild weakness, 9.46% moderate weakness and 4% suffered from severe weakness in the AoP group. On the contrary, the AoP group had about 35% respondents reporting of some sort of fatigue, which resonates with the existing understanding. This outcome suggests the possibility of a long-term protection provided by homoeopathic medicines in preventing post-COVID weakness.

The other common symptoms that have been reported by the patients in various studies were dyspnoea (43.4%) and joint pains (27.3%). This was seen amongst patients who complained of pneumonia or ARDS during COVID-19. Interestingly, amongst severe cases of AoH group of COVID-19 in our study, only 16.7% of cases still experienced dyspnoea and none was dependent on supplemental oxygen, while joint pains were experienced only by 6.7% of patients. Though the results on these were not found to be statistically significant, our study showed less prevalence of post-covid symptoms of dyspnoea and joint pains in AoH group.[xvi]

Further, a study by Angelo Carfi et al reported the presence of at least one symptom amongst 87.4% of patients after recovering from COVID-19.[vi] A study found that people struggling with shortness of breath (isolated dyspnoea) scored higher on the PCFS scale. This suggests the PCFS might also capture deconditioning, not just lung problems. Identifying a PCFS score that reflects a patient's acceptable level of function could be helpful. This would allow doctors to target patients who might need more extensive follow-up after COVID-19.[xvi]

The add-on Homoeopathy group of our study demonstrated a notable (72%) grade 0 respondents on the PCFS scale, compared to the placebo group (50%). Additionally, fewer patients were categorized as grade 4 in homoeopathy arm (11.83%) in comparison to the control group (16.22%).

It is pertinent to mention that a higher overall percentage of Grade 0 in respondents could also be attributed to the time lapse between the onset of symptoms and our survey period, which could lead to recall bias. Other confounders like varying severity of cases, treatment modality, different geographical conditions or the wave and stage of epidemic can also not be ignored. These are a few limitations of the study, and these factors can be counted in, and the results can be accounted for incidence in detail through meta-analysis of all post-covid studies.

Nevertheless, the outcomes of this cross-sectional survey point towards a long-term role of homoeopathic medicines in recovery and sustainability after acute infections such as COVID-19. Further in vitro studies to understand the effect of

these medicines on the biomarkers for long-term immunity may reveal more understanding of this therapeutic action. Also, clinical trials aiming long term, comparative follow ups of the patients who receive homoeopathic medicines during the acute infections that are known to bear chronic complications may be planned to throw more light on this subject.

Conclusion

When administered as an adjunct to standard care for COVID-19 patients, Homoeopathy seems to have contributed to enhancing overall functional status of the participants, even when the medication was discontinued a while ago. The survey, thus, suggests a possible role of Homoeopathy in improving overall immunity of the patients, which enables them to counter post-COVID weakness and other associated symptoms with greater strength, thus helping them regain independence in performing daily activities sooner.

Conflict of Interest

None declared

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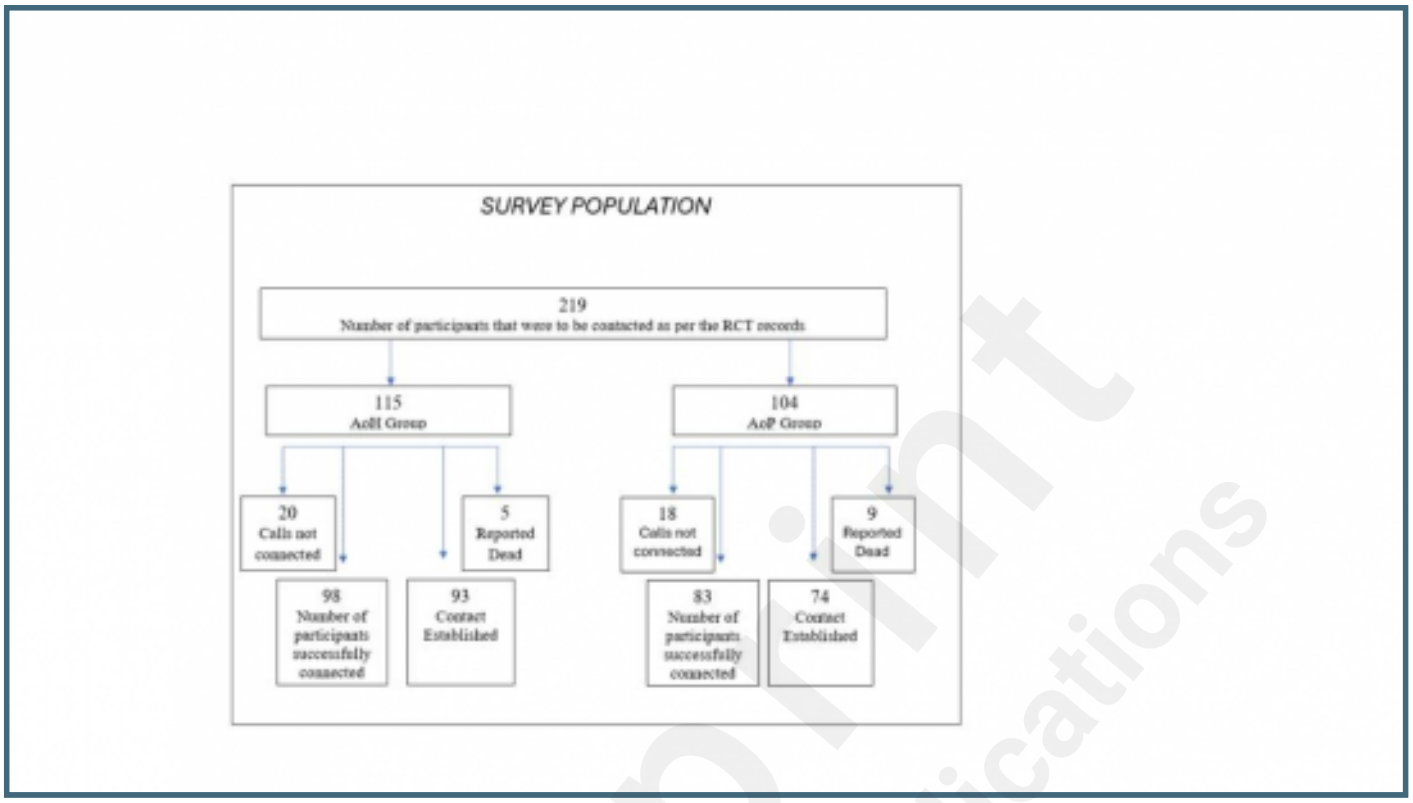
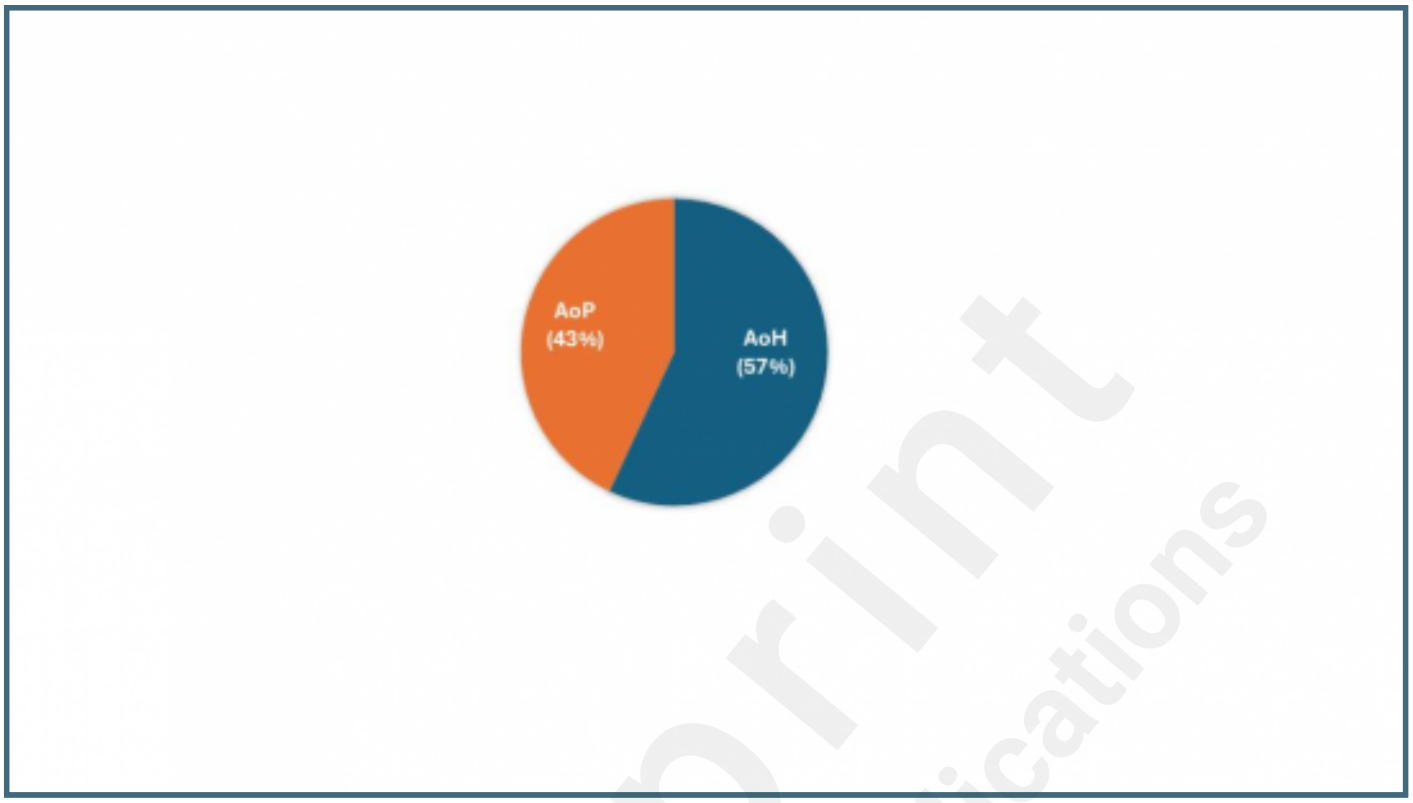
Supplementary Files

Figures

Flowchart depicting population surveyed.



Ability to do daily activities.



Grades of weakness among respondents.