Review Article

Expounding nested case control studies in the year of COVID-19: a scoping review and sub group meta-analysis

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ABSTRACT

Nested case control studies (NCCS) are mainly a type of cohort study due to its forward direction and temporality. This design is done only under two circumstances. a. disease must be new and rare in the population b. The diagnostic test must be fairly expensive. Thus, this study design is defined as 'a small case control study nested within a big cohort study'. The paper has expounded existing literature on nested case control studies by using scoping review and meta-analysis on hypertension sub-group. The data was systematically searched with following databases: Medline, NLM which had free articles and Google scholar. The aim of the study was to scope review of English language research papers from May 2020 to May 2021. 86 studies were excluded and 9 studies were selected after reviewing the title and abstract of 209 studies based on the PRISMA. The research has made a unique contribution, in a resource crunched setting, in expounding the study design implementations by lending critical viewing, theoretical revision and, new perspectives on use of nested case control studies in field settings.

Keywords: COVID-19, Nested case control studies, SARS-CoV-2, Scoping review

INTRODUCTION

The pandemic of COVID-19 or SARS-CoV-2.has created enough of fear psychosis and taken a heavy toll on human lives. Worldwide, 172,630,637 cases of COVID-19 by 6 June 2021, which were confirmed, and 3,718,683 deaths, reported to WHO. A total of 1,638,006,899 vaccine doses have been administered by 1st June 2021.[1] While the route of this outbreak is difficult to foresee, effective response requires immediate action from the view of classic public health strategies to the timely development and implementation of successful counter measures.[2]

In trying to understand the disease progression, the vast cohort bank and the ever-changing nature of the virus, several preclinical and clinical trials for single drugs or combinations are in passage of advancement.[3] It was essential to try and expound various nested case control studies being conducted under the auspices of COVID

positivity. Nested case-control study (NCCS) is an amalgamation of design of cohort and case-control. NCCS is mainly a type of Cohort study due to its forward direction and temporality.[4] This design is done only under two circumstances (a) disease must be new and rare in the population; (b) the diagnostic test must be fairly expensive. Thus, this study design was defined as 'a small case control study nested within a big cohort study'.

NCCS is different from pure form case-control study where in cases and controls are drawn from the population in a fully catalogued cohort.[5] The risk factor or exposure of interest is only measured among the cases and controls. NCCS is a more efficacious study as compared to a full cohort design.[6] In a nested case-control study the cases are drawn from a well-defined catalogued population and the controls are also taken from the same enumerated population. Thus, it is 'nested' in an existing preset same source population, which is COVID-19 positive patients, with known sample size. The term 'cohort' is commonly

referred to a group of sub research. There is no time prerequisite but defined by similarity in characteristics.[7] In nested case-control design, only data of a sample of the full study population needs to be retrieved and analyzed without having to do a new diagnostic study from the beginning. In the field of biomarker research, NCCS sampling has been identified as a useful design option within an enumerated cohort study.[8] The few advantages of NCCS are (a) problem of recall is eliminated; (b) abnormalities detected represents risk factors than the manifestations of early disease; (c) economical to conduct; and (d) greater comparability between cases and controls.[9]

The likely future emergence of pathogenic zoonotic corona viruses, its adverse economic impact as a pandemic and the and the lack of effective antiviral control plan of action have made it achingly clear that our preparedness to combat corona virus infections is extremely inadequate.[10]

METHODOLOGY

Search strategy and selection criteria

The present scoping review and meta-analysis is reported according to the Preferred reporting items such as (PRISMA) guidelines.[6] We searched Medline for studies published between May 2020-May 2021, with curtailment pertaining to language as only English language articles were included. A thorough search of the PMC literature was done to identify journal articles which had nested case control study as the study design in patients affected with COVID-19. The electronic databases Medline, and Google search, where only free PMC articles were searched for reviews published between 2020 and 2021. We did not consider articles that were referred by other researcher or identified in through cross references in included studies. Eligible studies were only Nested case control studies and pure study designs such as purely randomized control trials, case-control or cohort studies, and case series were not included except for references. We had to exclude review articles, case reports editorials etc.

Data were extracted from eligible articles only: The number of primary studies included in the review included the NCCS study design study population(s), interventions, therapy used, biomarkers and risk factors.

Three investigators (LT, AS, MJ) independently sorted and screened the journal titles and abstracts, and two (LT, MJ) independently sorted and screened full text papers. A third reviewer settled the discrepancies between reviewers at the abstract and full text stage. The use of a sensitive screening methodology at the title or abstract level wherein selection by at least two reviewers was adequate for a study to undertake full text review. In the scoping review all studies under the NCCS label were reviewed and among them those having a measure for hypertension were segregated for meta-analyses.

The keyword search was done using specific terms such as Nested case control study and COVID-19. All those studies which were published and available for free were included and those that were under publication were not included. The inclusion and exclusion criteria allow studies of 2020 to 2021 to be considered. We used the Review manager 5.4 for meta-analyses.

Patient and public involvement

Patients or any public outside of the mentioned researchers were not involved in the evolution of the research question or its progressive development in the actualization of the research, or in the devising of the manuscript at any stage. All authors have taken their study population from COVID confirmed or COVID-19 convalescent population.

RESULTS

The factors studied were 4 for, biomarkers, 2 for therapy and 3 were on risk factors. Table 1 shows study results conclusion and unit of study. The number of population under the predetermined cohort was 2214807 (twenty two lakhs, fourteen thousand and eight hundred and seven. the total sub set of population derived for study in a nested case control study is 10,078 (0.5%) of the cohort population. of the total population studied in the cohort 1128 (12%) were cases and 8950 (88%) were controls.

The statistical guidelines followed were, varied for example Fallerini et al used Lasso Log Regression, Fishers exact and unpaired t test. The association between the presence of TLR7 rare variants and severe COVID-19 was significant. Gnavi et al made use of Conditional log regression risks of CVi associated with drug prescription of ACEIs or ARBs, both were considered together then separately (accounting for switch of medication from one to other), neatly expressed as odds ratios and 95% confidence intervals. Gu et al used Mann Whitney U test, Clopper Pearson and MLR was used by Lewin et al.

The t test by Li et al, and Nemars, Wilcoxin signed rank test by Li et al. Youden index, conditional logistic regression and Bayes theorem was used by Planquette et al. Shi et al and Choi et al used Chi square and multiple logistic regression. In Figure 1, articles selected using PRISMA guidelines from Pubmed PMC articles, Google Scholar and Medline. Records excluded: N=18 not NCCS; N=8 not between 15 months COVID time; N=1 not COVID by d-dimer in DVT. Journal articles included in review with N=9, and records of included studies N=9. Figure 2 depicts sub-group meta-analysis measures hypertension. The four studies included were Gnavi et al, Gu et al, Planquette et al and Shi et al. Three studies were from the year 2020 and one from 2021. Total events in the cases were 197 and 710 in controls. The effect size was calculated for dichotomous variables where in the events were calculated and the OR obtained. The confidence interval is 1.18 (0.54, 2.60). Line of no effect is crossed by two studies Gnavi et al and Gu et al weighted at 30.0% and 27.4 % respectively. Z=0.41 (p=0.68), I2=87%.

Figure 3 is funnel plot showing the variability of individual studies (standard error). It is called a funnel plot because as the study size increases the standard error approaches zero. The funnel plot is symmetrical in its distribution with equal distribution above the mean and below the mean. The scatter within the funnel is evenly distributed and toward the tip of the triangle.
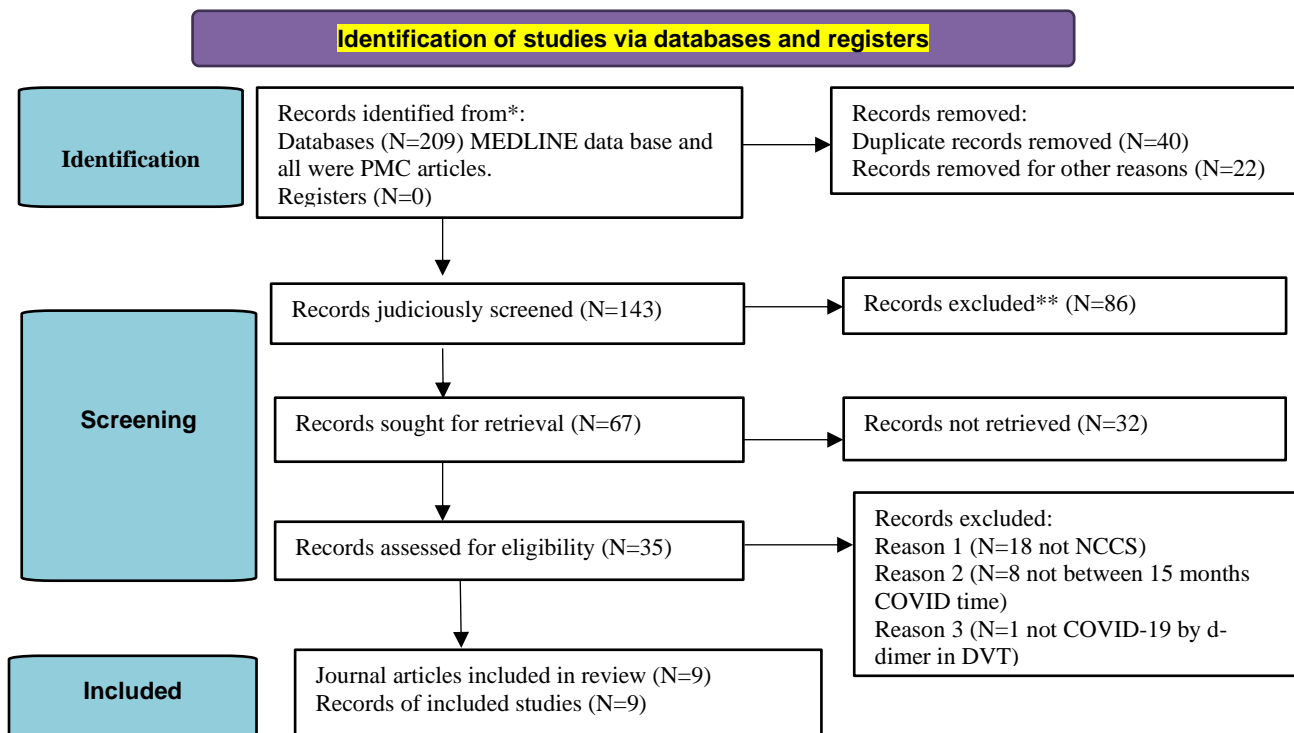

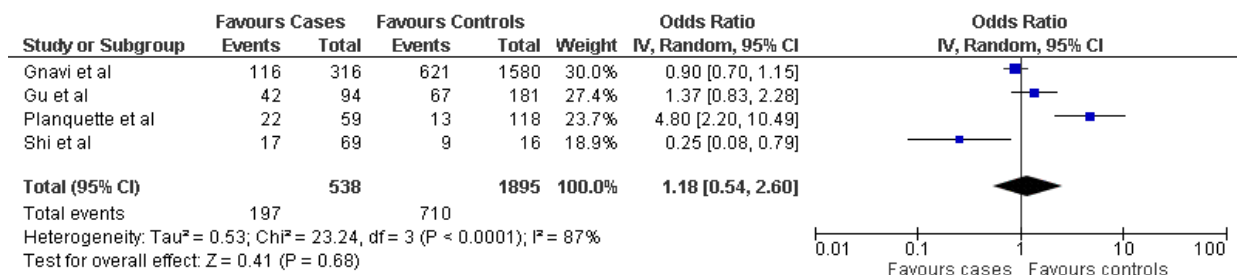**Figure 1: Articles selected using PRISMA guidelines.**

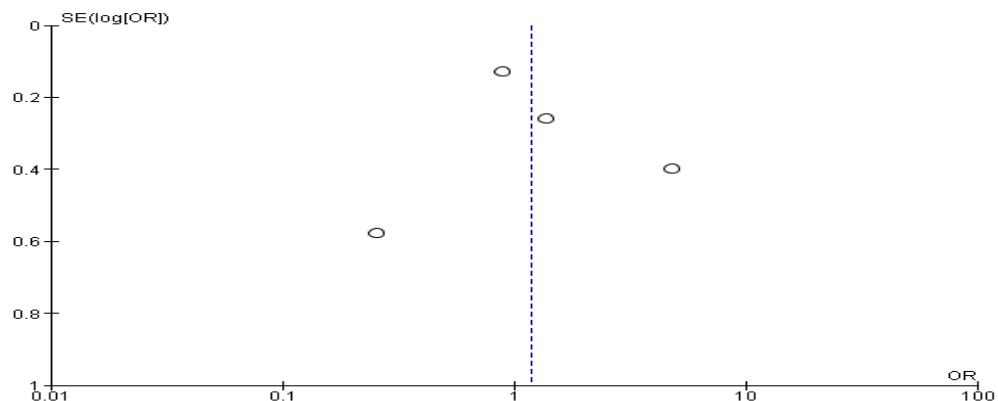**Figure 2: Forest plot showing meta-analysis of hypertension in COVID-19 cohort.**

Figure 3: Funnel plot of articles included in forest plot.

Table 1: Showing study results conclusion and unit of study.

S. no.	Authors	Results	Conclusion	Remarks
1	Fallerini et al[11]	TLR7 deleterious variants in 2.1% of severely affected males and in none of the asymptomatic participants. A reduction in TLR7-related gene expression in patients compared with controls demonstrating an impairment in type I and II IFN responses.	Severe disease COVID-19, susceptibility was seen to the tune of 2% in young males with TLR7 loss of function	Biomarkers
2	Gnavi et al[12]	In the HY population, ORs for ACEIs, ARBs, and the combination of the 2 were, respectively, 0.89 (95% CI, 0.70-1.15), 0.90 (95% CI, 0.70-1.17), and 0.78 (95% CI, 0.60-1.02). In the CDD population, ORs for ACEIs, ARBs, and the combination of the 2 were, respectively, 0.92 (95% CI, 0.64-1.32), 1.03 (95% CI, 0.70-1.50), and 0.95 (95% CI, 0.68-1.34).	There was no need to modify the present anti-hypertensive therapy, thus excluding a dose-response relationship.	Therapy
3	Gu et al.[13]	Of the 94 cases, the median age was 72.5 years old (IQR=16), and 59.6% were men, while in the control group the median age was 67 years old (IQR=22), and 64.6% were men. The estimated mortality risk in patients with pre-existing Coronary heart disease (CHD) was three times that of those without CHD (p<0.001).	Patients with pre-existing co morbidities, especially Coronary heart disease (CHD) need early intervention and extra care.	Risk factors
4	Lewin et al.[14]	A total of 7691 blood donors were included in the study. After adjustments, the seroprevalence rate was 2.2% (95%CI 1.9-2.6). Seropositive donors reported one or more symptoms in a proportion of 52.2% (95%CI 44.2-60.1); this proportion was 19.1% (95%CI 13.4-26.1) among seronegative donors, suggesting that approximately 50-66%. infections were asymptomatic.	In blood donors who are a fair representation of the population were significantly associated with seropositivity in Quebec.	Biomarkers
5	Li et al.[15]	Totally 82 patients (85.42%) showed complete lung inflammation absorption at the 84-day follow-up. On day 14, inflammation absorption at the 84-days follow-up. On day 14, the CM group had a signifies the CM group had a significantly higher absorption rate than the control group.	Intervention with Chinese medicine may also play a role in promoting the improvements of symptoms and lung inflammation in patients with COVID-19 with varying degrees of lung inflammation at the time of discharge.	Therapy
6	Li et al.[16]	The adjusted multivariable logistic regression analyses revealed that the independent risk factors associated with severe COVID-19 were CRP (OR 2.037, 95% CI 1.078–3.847, P = 0.028), SpO2 (OR 1.639, 95% CI 0.943–2.850, P = 0.080) and lymphocyte (OR 1.530, 95% CI 0.850–2.723, P = 0.148), whereas the changes exhibited by indicators influenced incidence of disease severity.	Potential indicators of severe COVID-19 found in this study are CRP levels and low SpO2, in patients independent of comorbid conditions, advanced age and sex. Males have a higher risk of developing severe symptoms of the disease as compared to females.	Biomarkers
7	Planquette et al.[19]	PE was suspected in 269 patients among 1042 COVID-19 patients, and confirmed in 59 patients (5.6%). Half of PE was diagnosed at COVID-19 diagnosis. PE patients did not differ from CT and CTPA controls for thrombosis risk factors. PE	In the whole population with covid 19 PE prevalence is around 5% and about 20% in clinically suspected. D-dimer can be a fairly reliable tool in diagnosis of oncoming PE	Risk factors

S. no.	Authors	Results	Conclusion	Remarks
		patients more often required invasive ventilation compared to CTPA controls (odds ratio (OR) 2.79; 95% confidence interval (CI) 1.33-5.84) and to CT controls (OR 8.07; 95% CI 2.70–23.82). PE patients exhibited more extensive parenchymal lesions (>50%) than CT controls (OR 3.90; 95% CI 1.54-9.94). D-dimer levels were 5.1 (95% CI 1.90-13.76) times higher in PE patients than CTPA controls.		
8	Shi et al.[17]	In multivariate logistic regression analysis, advanced age [Odds ratio (OR), 1.012; 95% Confidence interval (CI), 1.020–1.166; p=0.011) and the higher level of lactase dehydrogenase (OR, 1.012; 95% CI, 1.001-1.024; p=0.038) were independently associated with exacerbation in mild COVID-19 patients.	Among the mild patients, more attention should be paid by clinicians to the elderly patients or patients with high LDH levels.	Biomarkers and risk factors
9.	Choi et al.[18]	Use of ICS was associated with a significantly higher risk of mortality in the unadjusted analysis (OR, 3.11; 95%CI, 1.60-6.03; p<0.001), although the association was not significant after adjustment for age, sex, region, CCI, and hospital type (adjusted OR, 0.94; 95% CI, 0.43-2.07; p=0.88).	Only OCS was independently associated with mortality.	Therapy

DISCUSSION

Lasso regression is a fairly convenient balancing technique that reduces the model's complexity.[11] Fallerini's observation reported that screening in badly affected male patients with this specific marker for genetic disease to be started individual interferon treatment.[12] Similarly logistic LASSO regression model for diagnosing carcinoma supported radiologic findings and CDD was adopted by Kim et al.[13]

Conditional logistic regression or (CLR) is a special sort of logistic regression used when cases with specific conditions are each matched with n number of controls without the condition.[14] However the common design that is followed if 1:1 and if 1:N then the N may be between one to five. De et al calculated the OR and 95% confidence interval, adjusted for age sex, cardiovascular conditions and risk factors using conditional logistic regression.[15] No increased risk was observed with either angiotensin-converting enzyme inhibitors) or angiotensin-receptor blockers.

Multivariate logistic regression was used to find expressed ORs at 95%CI for determinants of COVID-19 associated hospitalization and mortality. Choi et al observed similar associations between risk of mortality and drugs used for respiratory diseases such as COPD, asthma etc. Oral cortico-steroids were independently associated with mortality.[16] It was also observed that prolong use of systemic corticosteroids in the COVID pandemic was associated with increased odds of COVID-19 related hospitalization in arthritic disease.[17]

Multiple log regression has been employed by Lewin et al where fever or sensation of chills or fever and loss or reduction in taste or smell were independently related to sero-positivity.[18] Shi et al used multivariate logistic analysis, and concluded that advanced age and therefore the higher level of lactase dehydrogenase were independently related to exacerbation in mild COVID-19 patients. Li et al also used MLR to point out that independent risk factors related to severeCOVID-19 were CRP, SpO$_2$, lymphocytes. Males had indicators showing higher levels in relation to myocardial injury, kidney injury or inflammations as compared in females.[19] Logistic regression models have been used for the different outcomes that were associated with the exposures of interest.[11,20] Mann Whitney U test is used by Gu et al for continuous variables and χ^2 or Fisher's exact test for binary variables.[21]

Clopper Pearson interval is a common method for calculating binomial confidence intervals.[22] It is by far the foremost covered confidence interval, but it's too conservative especially at extreme p values. Crude sero-prevalence rates and their respective 95% Clopper-Pearson CI have been calculated from the proportion of study participants who in the course developed antibodies against SARS-CoV-2.[18] In another retrospective study by

Szegdi et al with asymptomatic patients presenting for IVI the study included 279 cases and 319 controls. Of the many valid test done, only one SARS-CoV-2 positive patient was found, leading to a carrier rate of 0.36% with a 95% Clopper-Pearson CI of 0.01-1.99%.[23]

T test Fisher exact and chi square were used. Continuous variables have been compared using t tests, and categorical variables were compared using the χ^2 test or the Fisher exact test. Nemars counts are compared directly for matched cases.[24] Categorical variables were expressed in percentages (%). Continuous variables were expressed as median and Inter-quartile range (IQR), even if the information on traditional distribution was not evident Wilcoxon signed-rank test and paired t test were used as appropriately supported whether The Wilcoxon signed-rank test performs better than the paired t-test, and is more powerful in various conditions. It is based upon the sample standard deviation which is affected by outliers.[20] This study reveals decreased SpO$_2$, decreased lymphocyte counts and increased CRP levels, which form likely indicators of severe COVID-19, in patients without co-morbidities, advanced age and sex. Males were at higher risk of developing symptoms which were severe, of COVID-19 as compared to females.

Youden index is a abridged measure of the ROC curve. In this study Cases and controls have been matched in 1:2 ratio on the basis of centre of study, age and sex. It measures the effectiveness of a diagnostic marker and optimal threshold value (cut off point) for the marker.[25] Fluss et al (calculated as sensitivity+ specificity–1) was earmarked to get the adequate value of D-dimer peak levels. Planquette et al in their alternate calculation of the contingent probability is mentioned as Bayes Rule or Bayes Theorem.[26] The Positive and Negative predictive values (PPV and NPV) have been calculated with the Bayes' theorem with the PE prevalence within the whole cohort (5.6%) and CTPA (21.2%) within the cohort. In another study mortality of patients with confirmed PE on admission to the hospital was not statistically significant as compared to hospital mortality without PE (p=0.09) in whole group as the sample size in the study was small.[27]

For the sub group meta-analysis a forest plot revealed that the Random effects model was used due to the varying effect sizes crossing the no line of effect randomly. The pooled summary effect crosses the line of no effect numerically thus giving an eye ball effect of no significance at 95%CI. The summary effect is not statistically significant. Study heterogeneity is the measure in which the effect sizes vary in our study as they do not overlap with each other indicating high degree of heterogeneity.[28] The funnel plot depicting minimal bias in the studies chosen.[29] Though most common co morbidities that have categorically emerged are, hypertension and diabetes.[30] The relation of hypertension and COVID-19 patients could not be established in this review.

NCCS design

Fallerini et al studied 156 case who were hospitalised with endo-tracheal intubation and 77 control with no hospitalisation and oligo-symptomatic but the cohort of participants were compulsorily confirmed with RTPCR testing. Their limitation was low sample size and an preposterous conclusion of TLR7 screening for male patients to be started with interferon into the NCCS category.

Gnavi et al studied 316 and 171 cases of CVi, were matched with 1580 and 855 controls categorized for Hypertension and CDD respectively.[31] They concluded that there was no reason to modify the current antihypertensive therapy in confirmation to recommendations already given by major cardiological societies.

Gu et al 94 deaths were designated as cases and 1:5 proportions of controls 354 who were survivors matched by age and sex. Increased mortality risk in COVID-19 was calculated. They concluded that there was strong evidence of association between existing CHD and mortality risk for patients with COVID-19 infections.

Li et al did a retrospective nested case control studies were in the 67 cases were severe COVID patients and 67 controls were patients with moderate COVID-19. Definitions for cases ad controls have been clearly defined. They concluded that the predictors that potentially emerge are increased CRP levels and decrease in lymphocyte counts and SPO$_2$ which was independent of co morbid conditions, advanced age or sex.

Plaquette et al from cohort of COVID-19 patients they selected cases with CTPA proven PE N=59 and compared them to two sub group of controls matched for age, sex and center who were excluded or not suspected of PE with group 1- N=118, negative CTPA and group 2- N=118 with un-enhanced CT. They concluded that PE is markedly increased in clinically suspected population and D-Dimer to be an interesting diagnostic tool.

Questionable NCCS design

Lewin et al studied COVID patients in which 173 positive for antibody against 176 who were antibody negative they concluded that seroprevalence was much higher than cumulative COVID-19 incidence was relatively low. The study design was more confirmed to a case control study pattern and not and NCCS design. Li L et al tried to observe the effect of Chinese medicine where in 64 cases were administered CM and 32 were controls with or without CM and also included Western medicine (WM).[32] The distinction between case and controls is confusing though the cohort from whom the patients were drawn were COVID-19 positive. They concluded that intervention with Chinese medicine at the time of

discharge may promote improvements in lung inflammation and COVID related symptoms

Shi et al observed in a cohort of mild patients with their aim to identify high risk COVID-19 patients going into severe illness. 124 patients, 16 progressed to severe condition and 69 stable mild patients were studied. They fund that high LDH levels and advanced age were independent risk factor for deterioration form mild to severe progression. Even though the inclusion exclusion criteria do have an overlap the study has a prospective approach like in a nested case cohort study design. Index dates of matching of cases with controls have not been mentioned.

Choi et al design had a cohort of COPD in 640 COVID-19 patients as cases and 2560 non-COVID-19 patients for matched controls.In another cohort of asthmatic patients with COVID-19 were 90 and controls were 360 without COVID. They concluded that that ICS does not increase the risk of COVID-19 or its related mortality or respiratory outcomes. The study design is purely case control and does not fit in a NCCS design.

CONCLUSION

The scoping review for Nested Case control studies was carried out for a period of one year May 2020 to May 2021 done worldwide. The research has made an effort to present a unique contribution, in a resource crunched setting, in trying to expound the study design implementations by lending critical viewing, theoretical revision and, new perspectives on use of nested case control studies in field settings. Although the sub group meta-analysis for hypertension done with on random effect due to the high heterogeneity of included studies, the data has been presented in the form of forest plots. Depending on the data type various authors used means for normally distributed data of continuous variables otherwise, the Mann-Whitney test and Chi squared test was used for categorical variables and Fishers exact test when the data was small or limited. The forest plot displaying Odds ratio for events occurring among the cohort, it was found that pooled summary did not show significance of hypertension in COVID-19 patients in the nested case control studies thus deeming it inconclusive. There is a need for larger collection of Nested case control studies to come to a definitive conclusion. Nested case control studies reviewed do not seem to follow the criteria laid by case control studies but seem inclusive of cross-sectional or nested observational in the presence of an umbrella provided by the cohort.

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