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Influence of body mass index, height and hemoglobin A1c on nerve conduction study outcomes: a systematic review

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ABSTRACT

Background/Aim: Nerve conduction study (NCS) is a gold standard technique in assessment and diagnosis of nerve dysfunction. Despite diabetes and obesity are common accompaniment of peripheral neuropathy, their effects on NCS patterns have not been conclusively elucidated. Few studies have investigated contribution of biochemical and anthropometric factors as they affect interpretation of NCS. The aim of this study was to review the existing reports on the degree of correlation and impact of anthropometric and metabolic risk factors on NCS.

Methods: Systematic review.

Results: A total of 333 studies were searched of which 9 studies were included in this literature review, with three studies, each investigating the effects of BMI, height and glycaemic control on NCS outcomes. Glycaemic control was found to inversely correlate with nerve conduction velocity across both upper and lower limb nerve sites. This was also true when investigated as a categorical variable (p=<0.0001-0.03). Height also demonstrated a moderately inverse correlation to nerve conduction velocity in two studies (p= 0.01–0.05). However, BMI was found not to correlate with NCS outcomes.

Conclusions: Our results have shown that both glycaemic control and height influence NCS velocity and amplitude. The interpretation of NCS should therefore take these factors into consideration, possibly through the development of linear models accounting for height and HbA1c. These findings posit that improved glycaemic control would therefore also improve nerve conduction outcomes.

Keywords: Anthropometry, Diabetes, Nerve Conduction Study, Peripheral Neuropathy

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INTRODUCTION

Diagnosis of peripheral neuropathy requires careful clinical assessment and laboratory testing. NCS is commonly employed as an adjunct when the diagnosis remains uncertain [1, 2]. Electrodiagnostic tests such as NCS enable physicians to determine the pathophysiology of the neuropathy, in particular, distinguishing demyelination from axonal loss [3-5]. Testing also helps localize the site of the lesion, which is particularly helpful in determining whether the pathology involves the neuromuscular junction, peripheral nerve, the nerve root or anterior horn cells [3, 6-7]. During this process, a pair of electrodes is used, one to initiate an impulse, and the other to record the response (distally for motor, and proximally for sensory responses) [3, 5, 8].

Several retrospective and prospective experimental-designed studies have

conclusively elucidated the effects of age and temperature on NCS, particularly the parameters of amplitude and velocity of both motor and sensory nerves [4, 9-13]. These studies have demonstrated a direct, linear correlation between temperature and nerve conduction velocity [4, 9, 13]. Temperature is thus almost always accounted for when performing a NCS [4, 9]. Age has also been shown to reduce both nerve conduction amplitude and velocity, and is responsible for some variance in NCS outcomes [10-11]. However, there have been few studies investigating the biochemical correlation to NCS; with existing literature predominately focusing on diabetic-related measurements such as HbA1c and duration of diabetes [14-17].

The aim of this literature review was to evaluate the correlation of anthropometry and biochemistry to NCS amplitude and velocity of the upper and lower limbs from existing literature. The results obtained from this review will enable the analysis of factors responsible for variances in NCS outcomes. It is hoped that this will enable further research into determining possible anthropometric and biochemical factors affecting NCS outcomes and elucidate whether the development of predictive models taking into account these factors will be beneficial in the interpretation of NCS.

METHODOLOGY

Search Protocol

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analysis) was used as a model to guide selection of articles [18]. The terms: (nerve conduction* OR electrophy*) AND (correlation OR effect* OR influence) AND (sex OR height OR glycaemic control OR BMI OR body mass index OR duration of diabetes OR HbA1c OR thyro* OR vitamin b12 OR eGFR) AND (velocity OR amplitude OR latency) AND (neur*) were entered into PUBMED, EMBASE and MEDLINE (from January 1966 to December 2019). This search initially yielded 333 article titles with abstracts. The abstracts were screened by one author and of the 333 articles, 16 referred to NCS and anthropometric and biochemical correlation and were obtained. These articles were read in their entirety. Seven articles were inaccessible due to inaccessibility and were thus omitted from selection in accordance to point 1 of the exclusion criteria (Figure 1).

Inclusion Criteria

The inclusion criteria included publications comparing anthropometric and biochemical factors against outcomes of nerve conduction studies.

The inclusion criteria are as follows

1. Identifiable anthropometric/biochemical parameter used to determine NCS outcomes. This enables the analysis of data to see whether a correlation exists with said variable and NCS outcomes.
2. Limb temperature monitoring in studies measuring nerve conduction velocities. The speeds of motor and sensory nerves are temperature dependent.
3. Electrodiagnostic procedures are described in detail, to allow replication. A thorough description permits duplication of the study to re-produce and confirm the results.
4. Linear models used in the analysis of data. Consistency of data is important in the interpretation of results and cross- study analyses.
5. Cross-sectional and longitudinal studies both permitted.
6. Measurement of outcomes measured by one of/both p-value and correlation co-efficient. Using the same outcomes will enable comparison between studies.

The six criteria were printed on an article review template with a 'yes/no' option to be circled by the reviewer to indicate whether the article has entirely fulfilled each criterion. Articles must also not meet one or more of the exclusion criteria. A minimum of three studies is to be identified on one parameter before being eligible for analysis and discussion in the literature review. No language restrictions were placed on the search; however articles written in a language other english without translation were omitted as per point three of the exclusion criteria.

Exclusion Criteria

1. Article not readily available without significant expense.
2. Studies performed on non-human subjects.
3. Articles in a language other than English without provided translations.

Literature Review Process

The literature review was conducted such that it would allow others to access the same data to reproduce and verify the study's conclusions.

Selection of Studies

From the title, abstract and/or descriptors, one reviewer independently reviewed literature searches, reference lists and reviews to identify potentially relevant articles for review. Once literature was identified, one reviewer selected articles for analysis based on the inclusion criteria.

After independent evaluation of the articles, a second author verified the selection of the articles. A third author was not needed to arbitrate disagreement, however was available if needed.

Assessment of Quality and Risk of Bias

There is no single accepted tool available in evaluating the quality and bias of observational experimental studies. We therefore adapted pertinent recommendations from both ACROBAT (A Cochrane Risk of Bias Assessment Tool: for Non-Randomized Studies of Interventions) and STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) to establish an effective quality assessment tool used to assess the literature identified [18]. The appropriateness of the study design, study size, statistical methods, completeness of outcome data and reporting were analysed to determine the quality of the study. Each article analysed in the literature search was subsequently assessed using this method, as seen in Figure 2.

The assessment of quality for each component was based on an allocation of a score of 0 (inappropriate), 1 (appropriate to some extent) and 2 (highly appropriate); with a maximum total of 10 points. Two reviewers performed this review independently. Scoring differences of two or greater/less were resolved by a third reviewer.

Data Extraction

One author independently reviewed the titles and abstract of the articles identified in the systematic search and eligibility based on the specific inclusion criteria. The full texts of the literature chosen were obtained. Data was extracted in duplicate onto an excel spreadsheet.

Summary Measures

The measure of correlation was based on one of/both the p-value provided, in addition to the correlation co-efficient. These measured outcomes in the literature were used as a basis

of comparison between studies.

Design of Literature Review

The literature review was split up according to the biochemical or anthropometric parameter being assessed. Each section reports the results procured, with an ensuing discussion and appraisal of the literature.

RESULTS

The literature search yielded 333 articles with no duplicates. After a primary title and abstract screen, 16 articles remained for full text analysis. A total of 9 papers met all at least five of six inclusion criteria, without conflict with the exclusion criteria and were analysed as part of the literature review as shown in Figure 1.

Correlating Height to Nerve Conduction Amplitude and Velocity

Of the nine studies, three articles were identified in the literature search that assessed the correlation of height to nerve conduction parameters. Two studies were prospective, cross-sectional analyses, whereas one was a retrospective, cross-sectional chart analysis [5, 19-20]. All three studies used similar linear models to discern the correlation between height and nerve conduction outcomes, using the correlation co-efficient as a measure of correlation.

Rivner et al. assessed the correlation between height and nerve conduction through Pearson correlation co-efficient. This study was a retrospective, cross-sectional chart analysis of 3969 clinically normal subjects from a database of 22, 420 electrodiagnostic studies done between 1986 and 1998. The study demonstrated that both nerve velocity and amplitude are inversely correlated with height in the sural sensory, peroneal motor and ulnar motor nerves. It can be inferred that the strong correlation between height and the peroneal nerve velocity ($r= -0.42$) supports the hypothesis that nerve conduction velocities in the lower extremities have a stronger negative correlation with height than that of the upper limbs [20].

Height was shown to have a positive correlation to amplitude in the majority of motor nerves: right median ($r=0.545$, $p<0.01$), left median ($r=0.389$, $p<0.05$), right radial ($r=0.386$,

$p<0.05$), right tibial ($r=0.393$, $p<0.05$), left tibial ($r=0.349$, $p<0.05$), right common peroneal ($r=0.345$, $p<0.05$), left common peroneal ($r=0.366$, $p<0.05$), with the exception of the ulnar and left radial nerves. Although amplitude was strongly positively correlated to height, this was contrary to Rivner's findings where amplitude was moderately negatively correlated to height, in the same nerves (peroneal motor and sural sensory). On the other hand, there were no significant correlations identified between velocity and height in any of the motor or sensory nerves, with exception to the right and left ulnar nerves ($r= -0.536$, $p<0.01$ and $r= -0.430$, $p<0.05$ respectively) in Thakur et al. However, it is hard to discern too many conclusions from Thakur's study, given that results not statistically significant were omitted from display.

Correlating Glycaemic Control to Nerve Conduction Amplitude and Velocity

Three studies assessing the effect of glycaemic control on electrophysiological changes were identified in the literature search. All three studies used HbA1c as the determinant of glycaemic control. Two were cross-sectional analyses of glycaemic control [16, 21] whereas the other was a longitudinal study over a period of five years [15].

The longitudinal study performed by Huang et al. looked at fifty-seven type 2 diabetic patients with neuropathy [15]. Neuropathy was diagnosed based on having two or more, of the following four categories: symptoms, signs, previous nerve conduction studies and quantitative sensory testing. Nerve conduction was measured at the initial examination, and at follow up (24 ± 3.12 months). The changes in nerve conduction velocity were calculated as a percentage change in velocity based on the initial and follow-up recordings. Changes in amplitude were also assessed similarly. HbA1c was recorded at every three-month visit [15].

Tkac's cross sectional study also investigated the correlation of nerve conduction velocity and amplitude to HbA1c. Unlike Huang's study, Tkac measurements of outcome differed with HbA1c analysed as both a categorical and continuous variable. In univariate analysis, HbA1c was correlated against the sum of nerve conduction velocity (SNCV) and the sum of the distal amplitudes (SAMP).This was the only study in this review to summate the velocities and amplitude of the nerves measured into a composite measure [15-16]. SNCV and SAMP were both found to inversely correlate with HbA1c over the duration of the study

($p<0.0001$ and 0.0004 respectively). In multivariate analysis, HbA1c, duration of diabetes, height, sex and age were studied as independent variables.

Correlating BMI to Nerve Conduction Amplitude and Velocity

The systematic search yielded three articles focusing on the correlation between BMI and nerve conduction parameters. All three were designed as prospective, cross-sectional studies. Pawar and Buschbacher both evaluated BMI as a categorical variable in asymptomatic subjects, to illustrate the trend in measurements [22-23]. These measurements were taken from the median motor, ulnar motor, tibial motor, peroneal motor, median sensory and ulnar sensory nerves in both studies. Landau et al. investigated the correlation with BMI and nerve conduction velocity solely in the ulnar sensory nerve in both symptomatic and clinically normal patients [24]. Whereas the study by Pawar et al. consisted of 175 healthy, asymptomatic subjects [23], Buschbacher and colleagues study comprised of 253 healthy and asymptomatic volunteers free of any disease states with the potential to cause subclinical or clinical neuropathic symptoms [22]. Buschbacher et al. found that all sensory amplitudes varied with changes in BMI, and were inversely correlated with statistical significance ($p=0.0001$, 0.0001, 0.0011 at the sensory median, ulnar and sural nerves respectively).Pawar et al. had similar findings, however in the absence of statistical significance in the same nerves ($p=0.267$, 0.190, 0.528 respectively) [22-23]. Despite this, a noticeable trend showing decline in sensory amplitudes with increasing BMI was noted in both studies. The motor nerves in both studies however, demonstrated less of a correlation which was highlighted with less significant p-values in Pawar et al. ($p=0.738$, 0.593, 0.226, 0.144 in the motor median, ulnar, tibial and peroneal nerves respectively). Similar results were found in Buschbacher et al. ($p=0.2976$, 0.1286, 0.1175, 0.1144).

When compared to nerve conduction velocity, no demonstrable trends were shown between groups (both sensory and motor nerves) in both studies, with p-values reflecting such ($p=0.778$, 0.872, 0.569, 0.961 in the motor median, ulnar, tibial and peroneal nerves respectively in Pawar's study, and $p=0.5453$, 0.8612 in the motor median and peroneal nerves respectively in Busbacher's study). Contrary to Pawar and Buschbacher, Landau's retrospective chart analysis focused solely on the effect of BMI on the ulnar conduction velocity in symptomatic patients [24]. This study was based on the premise that extra adipose tissue over the ulnar nerve at the elbow provides protective padding and thus

decreases the likelihood of neuropathy [24]. In this study, no correlation was found between BMI and ulnar conduction velocity at the forearm (r = 0.01).

DISCUSSION

It is clear that the outcomes of NCS vary not only from technical, but also biological factors. In this literature review, we demonstrated that there was a correlation between height and glycaemic control directly correlated with nerve conduction amplitude and velocity. Conversely, BMI was not found to conclusively correlate with nerve conduction parameters.

Demonstrating an Inverse Correlation of Height to Nerve Conduction Amplitude and Velocity

Although conceptually similar, the results achieved were varied between the studies. Both Rivner et al. and Campbell et al. demonstrated a strong, inverse correlation between height and nerve conduction amplitude and velocity [19-20]. Conversely, Thakur et al. demonstrated conflicting results, depending on the site of the limb measurement [5]. However the differing designs of the study may be responsible for the results obtained.

The retrospective nature of the study by Rivner et al enabled a much larger power when compared to the other two studies. Both velocity and amplitude were demonstrated to correlate with height. It can be inferred that the high correlation between height and the peroneal nerve velocity supports the hypothesis that nerve conduction velocities in the lower extremities have a stronger negative correlation with height than that of the upper limbs. [20] This is possibly due to the greater anatomical variation in length in the lower limbs. These results were in keeping with the findings of Campbell et al, albeit a much lesser powered one. Conversely, Thakur et al demonstrated conflicting results, depending on the site of the limb measurement. Despite these discordances, two similar and well-designed studies came to the same conclusion. Thus, there remains substantial evidence demonstrating the correlation between height and nerve conduction outcomes.

Glycaemic Control –Inverse Correlation to Nerve Conduction Amplitude and Velocity

The results from Huang and group's study support the theory that poor glycaemic control is an important factor in the pathogenesis of neuropathy in diabetic patients [15]. The

deterioration in velocity was marked in subjects with a mean HbA1c greater than 8.5% over a two-year period. This is highly suggestive of a demyelinative change, given the profound negative correlation between HbA1c and velocity. Long-term hyperglycaemia appears less likely however, to cause axonal damage, given the insignificant changes to amplitude observed in the nerves measured. It must be kept in mind that this study was conducted over a two-year period and that differences in amplitude may take longer to manifest. It can therefore be inferred that velocity changes therefore appear to be a more sensitive index in this subset of patients. Clinically however, these changes are physically manifested nonetheless in patients with suboptimal glycaemic control. This is consistent with findings from both Munisekhar et al. and Katon et al. [21, 25].

Although having independent variables of slightly different parameters, there was also a noticeable trend between HbA1c and a decline in velocity in Munisekhar's study. There was also correlation with amplitude, with exception of the sural sensory nerve and peroneal motor nerve, which was only measured by Munisekhar et al., and therefore requires further investigation. However, the small number of subjects in Munisekhar's study (n=40) may also have predisposed to greater uncertainty, and thus, a lack of noticeable trend in amplitude. The cross-sectional design of Thakur's study also doesn't take into account the progression of nerve conduction parameters as mentioned previously, thereby possibly explaining the lack of trend with amplitude [21]. Despite this, all three studies demonstrated a strong, inverse correlation between nerve conduction velocity and glycaemic control.

No Conclusive Evidence Showing the Relation between BMI to Nerve Conduction Parameters

The results obtained from Pawar et al. and Buschbacher et al. assessing BMI categorically were varied. A mild decline in sensory amplitudes with increasing BMI was observed, however in the absence of statistical significance. This suggests that BMI may have limited to no impact on the outcome of sensory nerve conduction amplitudes. Motor amplitudes were found not to demonstrate any correlation with BMI, with no identifiable trends in either study. Similar to its sensory counterparts, this lack of a correlation could possibly be due to lower baseline amplitudes in motor compared to sensory nerves. Therefore, a decrease in motor amplitude proportionate to the decrease in sensory amplitude is more

likely to have a less profound effect [22-23]. Despite the lack of statistical significance in the study by Pawar et al., a modest, but noticeable increase in velocity was observed in patients of BMI 23-27.9 in all nerves with the exception of the peroneal motor and median sensory nerves. Although nerve conduction velocity was only measured and thus comparable in the peroneal motor nerves, similarly, p-values of 0.861 and 0.961 suggest statistical insignificance [23]. On the other hand, the findings in Landau's study were mixed, with BMI shown to directly correlate with ulnar nerve velocity across the elbow where the subcutaneous tissue is presumably protecting the nerve from external compression. However, ulnar nerve velocity was not found to correlate with BMI when measured in the forearm – similarly investigated in the other two studies [24].

It is interesting to note that the methodology used in all three studies was similar, thus eliminating the need to take design and outcome into account when interpreting results. However, critical analysis revealed none took these factors into account for possible variance in the results. The analysis of the three studies demonstrated limited correlation between BMI, nerve conduction velocity and amplitude, with some discrepancies in findings. Notwithstanding, the findings suggest that BMI is not correlated to NCS amplitude or velocity.

CONCLUSION AND FUTURE DIRECTIONS

The effects of height, BMI, and glycaemic control on the outcomes of the NCS have been explored in this review. There is convincing evidence that HbA1c, as a measurement of glycaemic control, is strongly, inversely correlated with nerve conduction velocity. The relationship was shown using HbA1c as a continuous and categorical variable, with the most significant differences demonstrated with HbA1c of greater than 7-9%. Height was also found to inversely correlate with both velocity and amplitude in two of the studies, despite inconclusive results from a third study. BMI however was not found to correlate with NCS outcomes in any study, with poor correlation coefficients and a lack of any significant results.

The scientific and statistical techniques used in the reviewed literature should also be taken into account in the development of future studies into NCS. Linear models with univariate correlation analyses were most commonly used. Multivariate analysis of variables identified

to be significant in univariate analysis should also be employed to account for individual variance, with regards to NCS outcomes. This demonstrates the potential for further research into biochemical factors and their influence and correlation on the outcomes of NCS, especially focusing on factors not identified in the literature search.

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DECLARATION OF COMPETING INTEREST

All authors declare no conflicts of interest.

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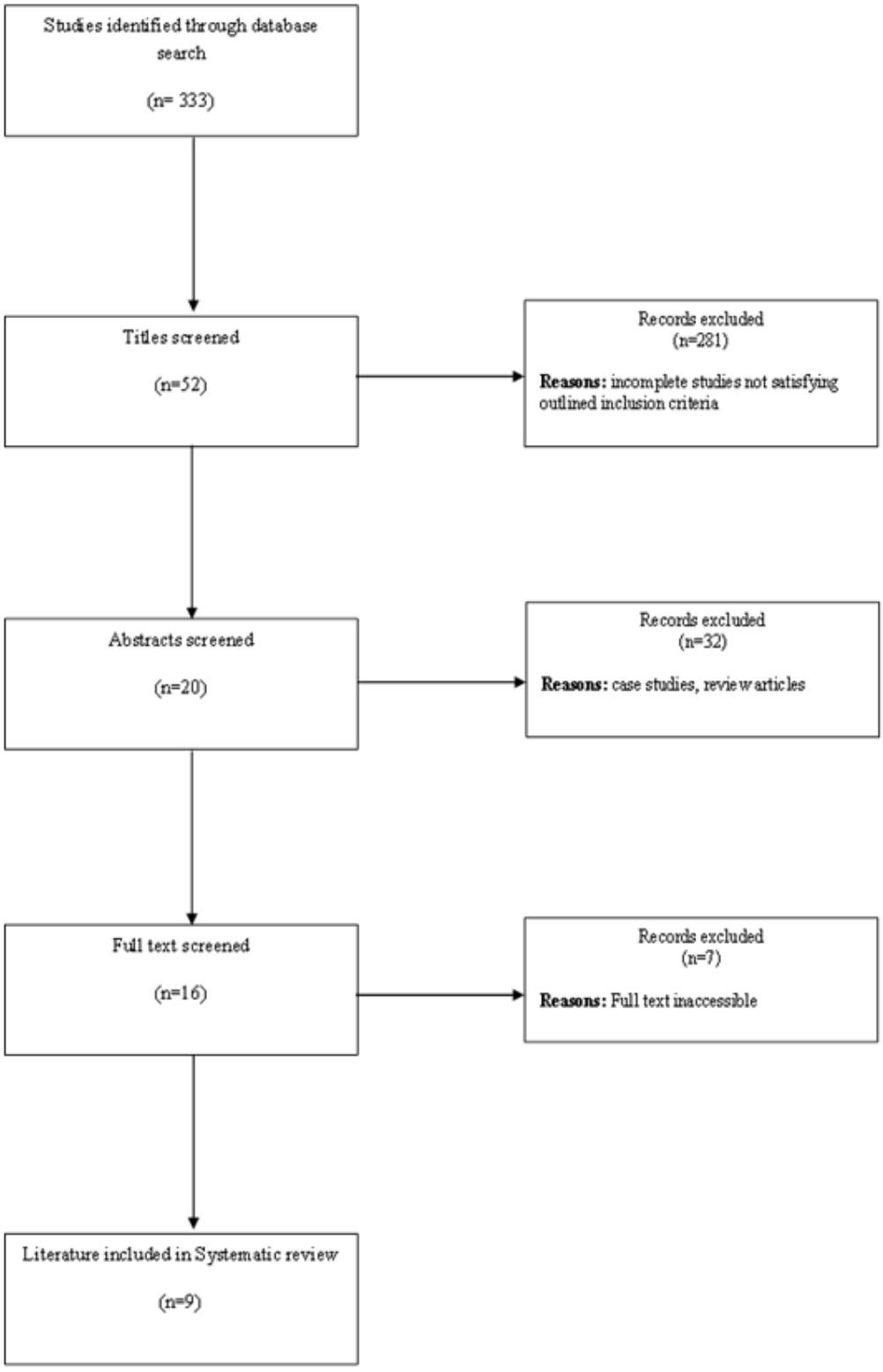

Figure 1. Search Methodology, based on PRISMA guidelines [18]

Quality Assessment Score

0 = Inappropriate 1 = Appropriate to Some extent 2 = Highly Appropriate

STUDY	STUDY DESIGN	STUDY SIZE	STATISTICAL METHODS	COMPLETION OF OUTCOME DATA	FREE OF SELECTIVE OUTCOME REPORTING	TOTAL
RIVNER – 2001 USA	2	2	2	2	2	10
CAMPBELL – 1981 USA	2	1	1	2	2	8
THAKUR – 2011 NEPAL	1	1	2	1	1	6
HUANG – 2005 TAIWAN	2	1	2	2	2	9
TKAC – 1998 CANADA	2	2	2	2	2	10
MUNISEKHAR – 2011 INDIA	1	1	1	1	2	6
BUSCHBACHER – 1998 USA	2	2	2	2	2	10
PAWAR – 2012 INDIA	1	2	1	2	2	8
LANDAU – 2005 USA	2	1	2	2	2	9

Figure 2. Quality Assessment of Studies