

**TOPIC: “A comparative study of cognitive function, pre-operative and post-operative, in patients undergoing valvular heart surgery.”**

## INTRODUCTION

1  
2 The recognition of neurological complications associated with cardiac surgery has been  
3 reported since the dawn of the specialty. Neurological dysfunction includes a spectrum  
4 which ranges from neurocognitive dysfunction to cerebrovascular accidents. Cognition  
5 is defined as process of perception, memory and information processing which allows  
6 the individual to acquire knowledge, solve problems & plan for future. Cognitive  
7 dysfunction is thus impairment of these processes.

8 Post-operative cognitive dysfunction (POCD) has been documented after major  
9 surgeries both cardiac and non-cardiac. With improvement in surgical & anaesthesia  
10 techniques survival after major surgeries-cardiac as well as non-cardiac has improved &  
11 thus post-operative comorbidities have gained major attention which includes POCD,  
12 which may affect quality of life of patients after surgery. Incidence of POCD after cardiac  
13 surgeries worldwide as indicated by previous studies ranges from 5 to 40 percent within  
14 first post-operative week. Indian population data is not accurately available for POCD.

15 Over time, the demographic characteristics of patients undergoing cardiac surgery  
16 have shifted to include a higher proportion of elderly patients, undergoing increasingly  
17 complex procedures. The average age of cardiac surgery patients has increased from  
18 ~64 years in 2001 to ~67 years in 2010. The number of patients with neurological  
19 disease prior to surgery has nearly doubled from 1.4% in 2001 to ~2.8% in 2010.  
20 Cardiac surgery procedures have also become more complex, with the number of  
21 patients undergoing isolated valvular heart surgery, decreasing by almost 20% from  
22 2001 to 2010. Despite higher patient risk profiles,  
23 the mortality rate has fallen slightly from 4.0% in 2001/2002 to 3.1% in 2010/2011  
24 (National Cardiac Surgery Audit, UCL, 2012).

25 POCD may range from short term cognitive changes affecting memory & visuospatial  
26 functions to post-operative delirium & dementia. But the most common complaint in the

27 first few weeks following valvular heart surgery relates to memory. The recognition of  
28 such cognitive changes by patients, families, and physicians led to a series of studies in  
29 which different areas of cognitive performance were tested before and at varying times  
30 after valvular heart surgery. Verbal, visual & tactile perceptions, intellectual performance  
31 like calculation & retention, speaking etc. forms constellation of features in early post-  
32 operative period while affection of thought processes like insight may be affected in long  
33 term. Pre-operative co-morbidities like diabetes, hypertension, and history of stroke are  
34 associated with an increased risk of POCD as documented by previous studies.  
35 Patients with impaired cognition pre-operatively or those having neurological diseases  
36 are at increased risk of POCD. An early assessment of cognitive function, after the  
37 surgical stress & effect of anaesthesia wean off, may be useful in early diagnosis of any  
38 cognitive changes if present. If there are any changes which may affect the cognitive  
39 functions of the patient timely remedial measures may be instituted.

40 It is therefore of paramount importance, to determine the etiology and the extent of brain  
41 injury leading to complications which may vary from subtle cognitive impairment to  
42 catastrophic stroke events.

43 The present study is an attempt to assess the cognitive function of patient  
44 undergoing valvular heart surgery using cardio-pulmonary bypass before and after the  
45 surgery.

46 The Hindi mini mental scale has been used for the assessment of POCD in the study. It  
47 is a rapid screening battery, to explore different cognitive domains: attention/orientation,  
48 memory, fluency, language and visuospatial Hindi mini mental scale. is considered  
49 useful in discriminating cognitively normal subjects from patients with mild dementia.

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## **AIM & OBJECTIVES**

56 **Aim: -**

57 To test occurrence of early post-operative cognitive dysfunction after valvular heart  
58 surgery using bypass machine in patients having normal cognitive function pre-  
59 operatively.

60 **Objectives: -**

61 1. To assess the cognitive function of patient undergoing valvular heart surgery using  
62 cardio-pulmonary bypass one day prior to surgery.

63 2. Reassessment of patient's cognitive functions 72 hours post-operatively.

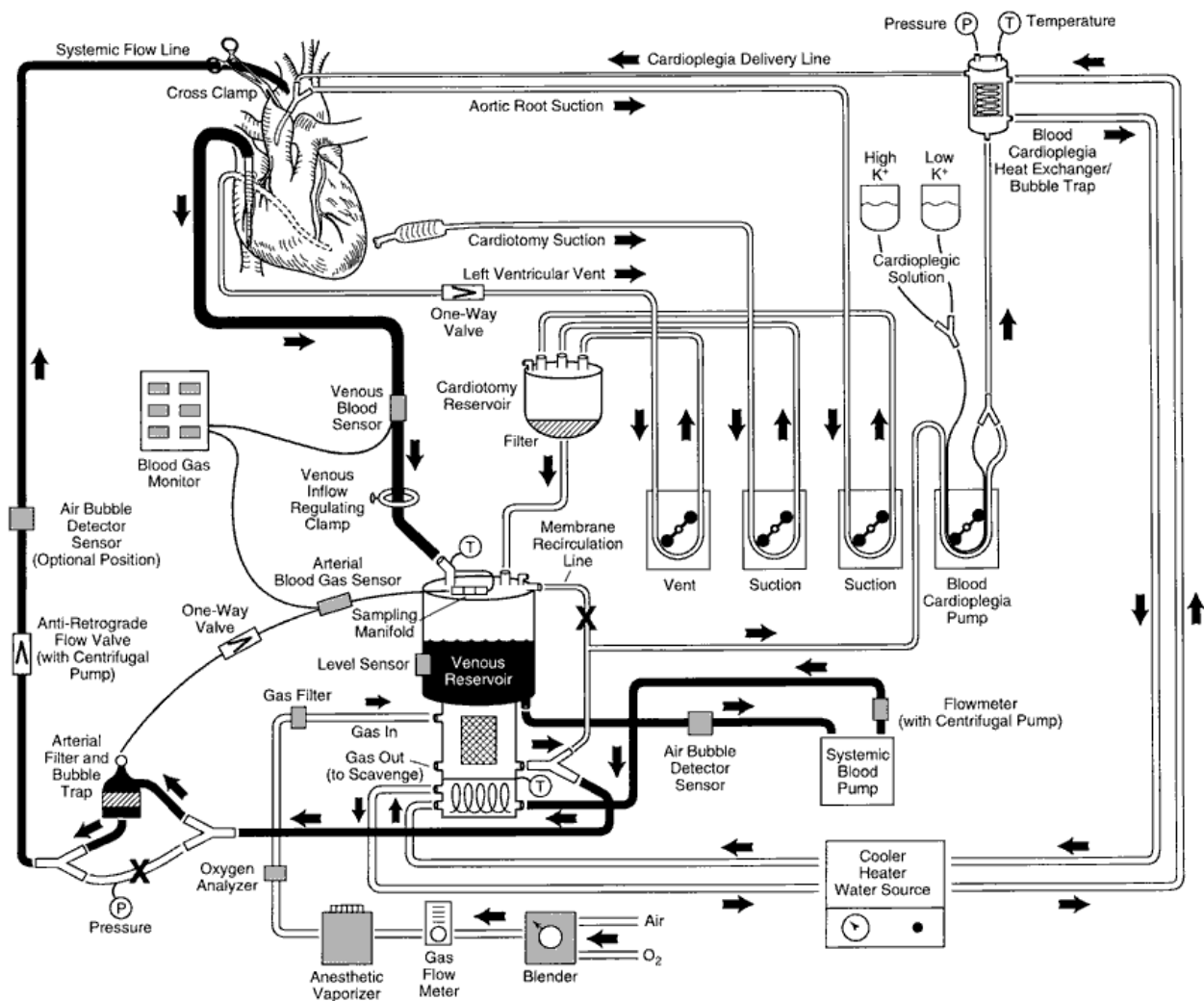
64 3. To compare the patient's pre-operative assessment of cognitive function before  
65 surgery with their post-operative assessment.

## 66 **PATHOPHYSIOLOGY**

67 The exact pathophysiology of POCD remains undefined. Previous studies on POCD  
68 have focused on investigating the risk factors associated with early POCD. Table 1  
69 describes the variables that have been shown to be associated with early/intermediate  
70 POCD. In terms of patient-related baseline factors, or sometimes called predisposing  
71 factors, increasing age and lower levels of education have been identified as the main  
72 ones in the early study by the International Study on Postoperative Dysfunction  
73 (ISPOCD) <sup>[33]</sup> In a subsequent study by Johnson et al <sup>[34]</sup> that included only a subset of  
74 the population reported in the initial study, alcohol intake was determined to be a  
75 predisposing factor for POCD. Preoperative impaired cognitive status also has been  
76 shown to be associated with POCD <sup>[35]</sup>

77 Whether patients have a genetic predisposition for development of POCD is not well  
78 understood because findings from studies to date are conflicting.

79 Methodological differences between delirium and cognitive assessments, difference in  
80 the timing of assessments, and potential differences in patient populations among  
81 different studies may result in differences in the findings. Following factors are  
82 implicated in the development of POCD



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**TABLE 2**

**Risk factors for postoperative cognitive dysfunction (POCD)**

Risk factors	
Patient	advanced age; pre-existing cerebral, cardiac, or vascular disease; preoperative mild cognitive impairment (MCI); low educational level; history of alcohol abuse
Operation	extensive surgical procedure, intra- or postoperative complications, secondary surgery
Anesthesia	long-acting anesthetic, marked disturbance of homeostasis, organ ischemia due to hypoxia and hypoperfusion, intra- or postoperative anesthesiological complications

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**86 VALVULAR HEART SURGERY AND POCD**

87 Most frequently described mechanism of brain injury in valvular heart surgery is based  
 88 on the recognition that micro emboli are generated by the surgeon manipulating the  
 89 heart and aorta, through cardiomy suctioning, and by the cardiopulmonary bypass

90 Circuit itself. Micro emboli can be detected intraoperatively as high-intensity transient.  
91 signals by trans cranial Doppler sonography. They have the potential to lodge in  
92 cerebral microvasculature, impairing blood supply to the brain and thus cerebral  
93 oxygenation. Several phases during cardiac surgery have been associated with  
94 increased risk of embolic showers. Aortic cannulation and clamping (during application  
95 of cardiopulmonary bypass) increase the high-intensity transient signal rate, particularly  
96 if there is extensive atheroma in the ascending aorta.<sup>[61]</sup> It is not surprising, therefore,  
97 that most (81%) micro emboli are generated at the point of aortic cross-clamp  
98 release.<sup>[62]</sup> Retaining the shed mediastinal blood with cardiotomy suckers provides an  
99 additional source of lipid emboli and other fragments,<sup>[63]</sup> which can be returned into the  
100 circuit and onto the brain. Furthermore, a variety of particulate matter and air emboli are  
101 generated within the cardiopulmonary bypass circuit itself. These can be filtered before  
102 blood is returned to the patient with the assumption that fewer micro emboli then travel  
103 to the brain. The use of cell salvage techniques by which red blood cells are filtered and  
104 washed before being returned to the circulation may help, but this has shown no  
105 specific neurological benefit or reduction in POCD, and, indeed, that it may disrupt  
106 coagulation <sup>[63]</sup>. Whatever the mechanism, there is apparently no straightforward  
107 association between the number of micro emboli released and postoperative  
108 pathological changes found on brain imaging or incidence of POCD.<sup>[64,65]</sup> In addition to  
109 Studies targeting the identification of risk factors of POCD, recent investigations have  
110 focused on identifying the pathophysiology for POCD

111 VALVULAR HEART SURGERY is a major surgery which results in a complex systemic  
112 response, which includes neuro inflammation. <sup>[52]</sup> Both systemic and neural  
113 inflammation, which occurs because of surgery, may directly affect patient outcome. For  
114 example, blood loss and tissue injury might affect the immune system to produce an  
115 inflammatory response.<sup>[53]</sup> Data from preclinical studies support the concept that  
116 inflammation is a possible pathogenic mechanism for POCD, and cytokines such as  
117 interleukin-1 $\beta$  have been implicated.<sup>[54,55,56]</sup> However, the clinical relevance of these  
118 experimental findings remains to be determined. Future studies using translational and  
119 multidisciplinary approaches are indicated to determine the role of inflammation as a  
120 possible causative factor in the pathophysiology of POCD...Numerous studies over the

121 past decade have reported an acute change in cognitive status in adult patients after  
122 major surgery. Most evidence suggests that these early cognitive changes are transitory  
123 and do not persist in the long term. However, the prognostic significance of POCD  
124 remains a hotly debated topic, especially considering recent data showing that patients  
125 with early POCD were at higher risk of morbidity after discharge. Furthermore, whether  
126 patients with early POCD have preexisting mild cognitive impairment and experience a  
127 steeper downward cognitive trajectory independent of the effect of anesthesia and  
128 surgery is another question that warrants further investigation. It is anticipated that  
129 future studies will elucidate better the pathophysiology of POCD using large sample  
130 sizes and longitudinally collected patient data in both the early and late postoperative  
131 period. Thus, to conclude many risk factors for development of POCD have been  
132 identified but exact pathophysiology is yet to be established

## 133 **MATERIALS AND METHODS**

### 134 **Study Design:**

135 It is a cross sectional study.

### 136 **Ethics:**

137 The study initiated after obtaining necessary permission from the institutional ethics  
138 committee. It is done only after obtaining informed consent from the study participants  
139 who fulfill the inclusion criteria for the study.

### 140 **Study Population:**

141 The study population consisted 110 patients of age group 25-65 years who underwent  
142 Valvular Heart Surgery using cardiopulmonary bypass machine who fulfilled the criteria  
143 for the participation in the study.

### 144 **Place of Study:**

145 Cardiovascular & thoracic surgery ward & recovery room in a tertiary care hospital in  
146 the Metropolitan city in Maharashtra.

147 **Duration of Study:**-Study was conducted over a period of one year.

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### Details of study procedure:

149  The study was conducted after approval of Institutional ethics committee.



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151  Each patient was visited one day prior to surgery in the wards.



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153  The procedure to be done was explained to the patient in their understandable  
154 language and a written informed consent obtained for participation in the study.



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156  A structured questionnaire that is Hindi Mini Mental Scale was used to know pre-  
157 operative cognitive function of the patient.



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159  Same questionnaire was used 72 hours after operation and results compared to  
160 assess the cognitive dysfunction in study subjects in the postoperative period.



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162  Training to apply and interpret Hindi Mini Mental Scale was taken from Neuro-  
163 psychologist.

#### 164 **A. Sampling method:**

165 Study population selected by non-probability convenience sampling method.

#### 166 **B. Inclusion criteria:**

167 • Patients undergoing Valvular Heart Surgery with use of bypass machine intra-  
168 operatively.

169 • Patients in whom anaesthesia is reversed & patients extubated at or before 24 hours  
170 of surgery.

171 • Age: 25 – 65 years

172 • Sex: Male and Female

173 • On pump time, less than two hours

174 • Patients years of education more than 4 years and able to comprehend the test

### 175 **C. Exclusion criteria:**

176 • Refusal by the patient

177 • Patients having significant neurological deficit pre-operatively

178 • Patients with known psychological illness or those with cognitive dysfunction at  
179 baseline assessment.

180 • Patients having any difficulty in talking or affected speech.

181 • Patients on any sedation at or after 24 hours of surgery.

### 182 **D. Sample size calculation**

183 Sample size was calculated by using the Formula<sup>64</sup>

$$\text{Sample size (n)} = \frac{Z^2 (1-\alpha/2) \times P * Q}{d^2}$$

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185 Considering variations in POCD prevalence in different studies for early cognitive  
186 dysfunction, prevalence of POCD (P) was considered as 7% as observed in the study

187 [67]

188 P= 7%

189 Q=100-P = 93%

190 Z is the value of Z score at 95% confidence interval = 1.96

191 d= Absolute precision required on either side of the proportion (in percentage points) =

192 5 percentage points

193 Calculated sample size: N=99.99= 100



194 Therefore N= 100, so sample size is taken as 110 considering drop outs (10%).

195 **Tool for study:**

196  Hindi Mini Mental Scale is a rapid screening battery, including five subscales to  
197 explore different cognitive domains: attention/ orientation, memory, fluency, language  
198 and visuospatial ability.

199  HMMS is considered useful in discriminating cognitively normal subjects from  
200 patients with mild dementia.

201  HMMS was used one day prior to surgery and only those patients were included  
202 in study who had normal HMMS score that is less than -1.5 standard deviation for years  
203 of education.

204  The repeat assessment was done on 72 hours of surgery and value less than -  
205 1.5 standard deviation for years of education is taken as normal while value more than -  
206 1.5 standard deviation is indicative of POCD

207  Post-surgery score was compared with the baseline score & any significant  
208 difference if present was noted.

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### Results and Observations

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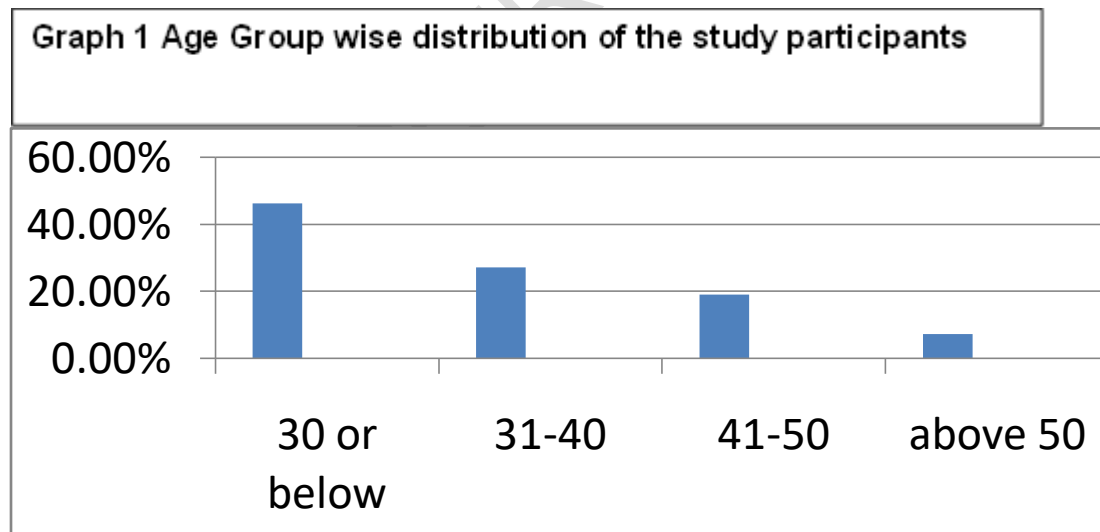
**Table 1 Age Group wise distribution of the study participants**

Sr. no	Age group ( years )	No. of study participant
1	30 year or below	51 ( 46.36% )
2	31-40	30 ( 27.27% )
3	41-50	21 ( 19.09% )
4	Above 50	8 ( 7.27% )
TOTAL		110

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228 The above table shows the age wise distribution of study subjects. Total 110 cases  
 229 were studied out of which 51 were below 30 years of age comprising 46.36% of study  
 230 subjects, 30 were between 31 to 40 years of age comprising 27.27% of the study  
 231 group.21 subjects that is 19.09% of study group population was of 41 to 50 years and 8  
 232 (7.27%) were above 50.

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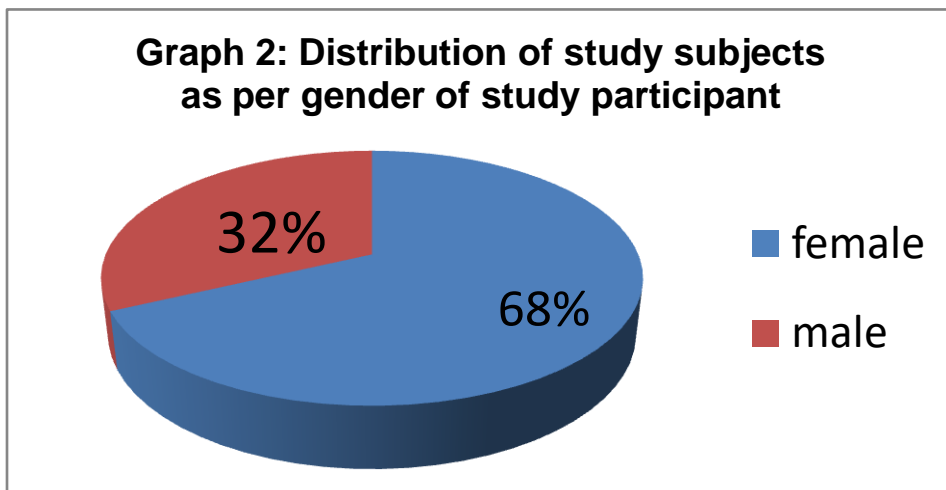
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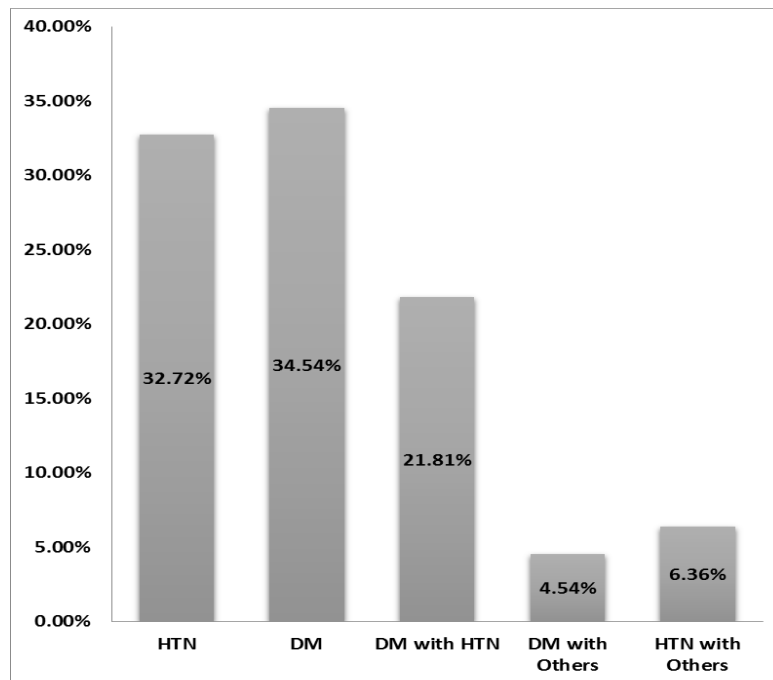
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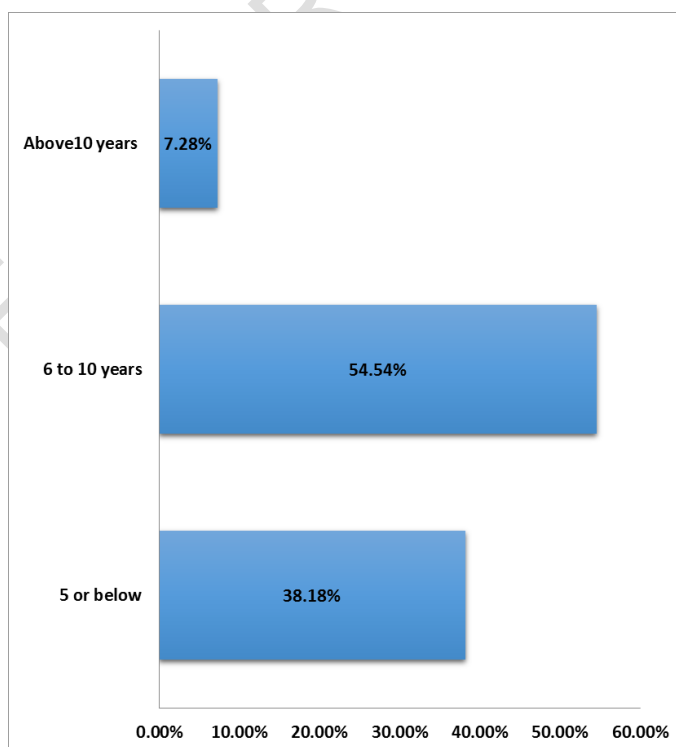
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241 **GRAPH 3: Distribution of study subjects as per Associated Co-**  
242 **morbidities**



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246 **GRAPH 4- Distribution of study subject as per duration of associated**  
247 **co- morbidities**

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250 **Table 2: Distribution of study subjects as per presence of POCD**

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Sr. No.	Presence of POCD	No. of Study Participants
1	Yes	02(1.82%)
2	No	108(98.18%)
<b>Total</b>		<b>110</b>

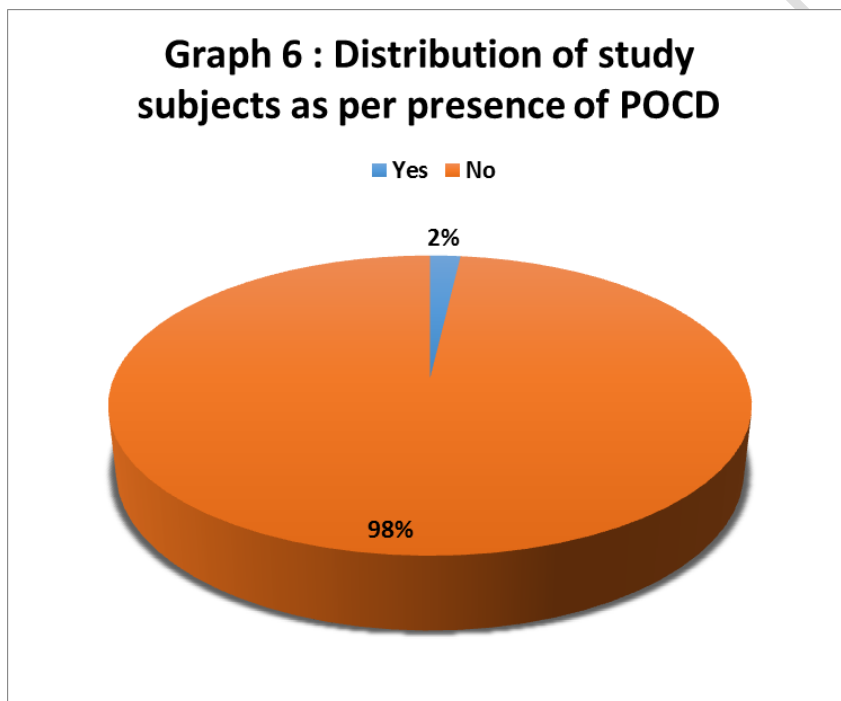
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259 **Table 3: Sex wise distribution of study subjects as per presence of**  
260 **POCD**

Sr. No.	Sex	Presence of POCD		Total
		Yes (%)	No (%)	
1	Female	01(1.34)	74(98.66)	<b>75</b>
2	Male	01(2.86)	34(97.14)	<b>35</b>
	<b>Total</b>	<b>02(1.85)</b>	<b>108(98.15)</b>	<b>110</b>

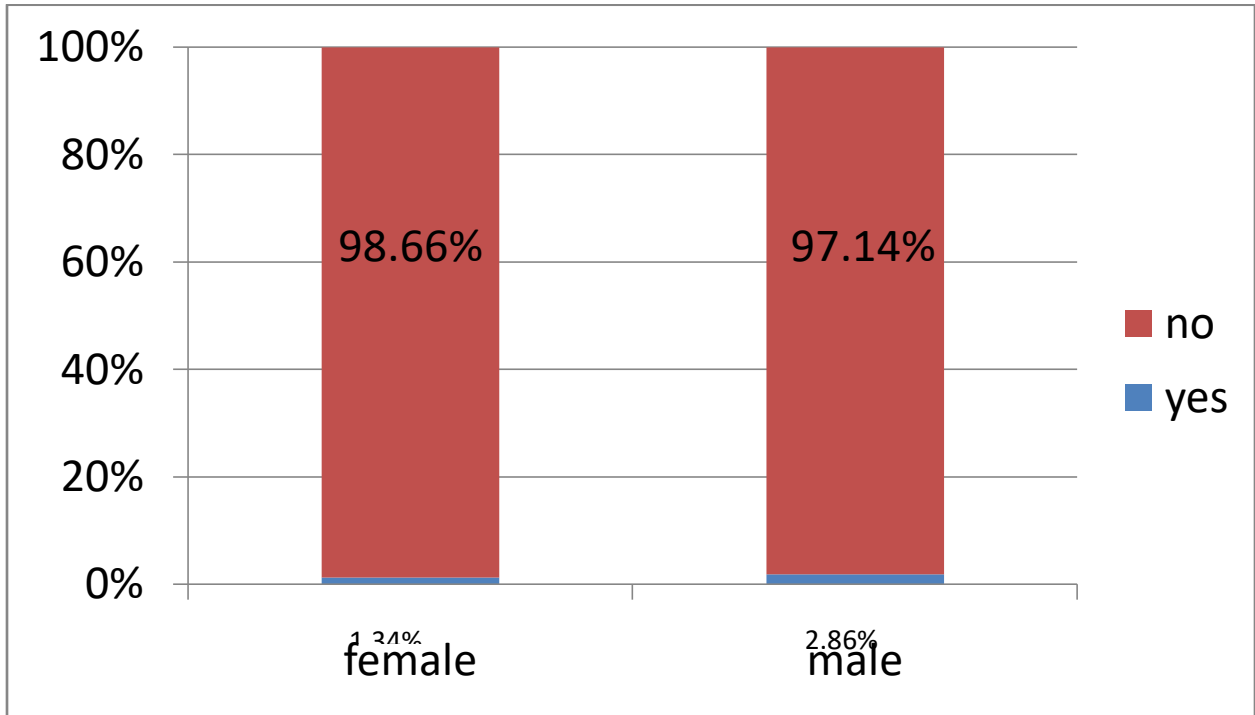
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264 **GRAPH 7: Sex wise distribution of study subjects as per**  
265 **Presence of POCD**

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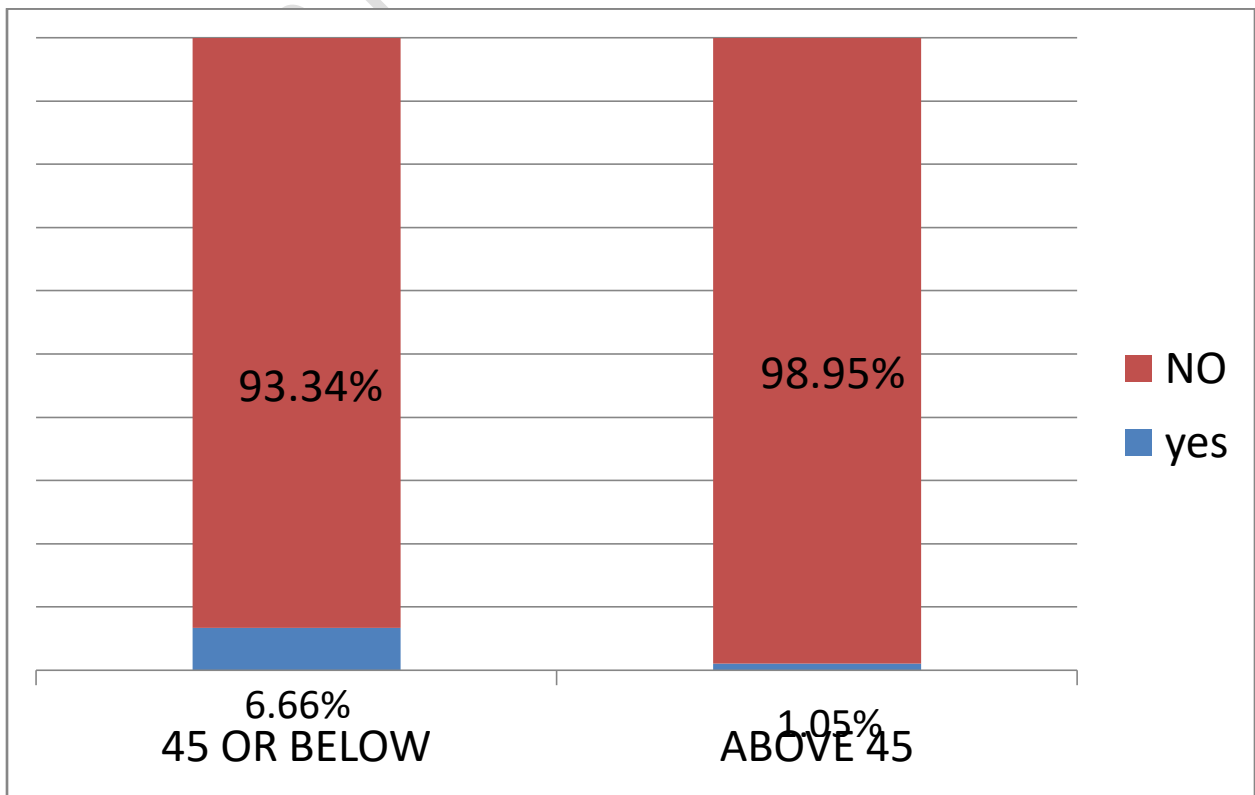


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268 **GRAPH 8: Distribution of study subjects as per presence of POCD**  
269 **and age Group**

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## Discussion

273 Post-operative cognitive dysfunction (POCD) has been documented after major  
274 surgeries both cardiac and non-cardiac. With improvement in surgical & anaesthesia  
275 techniques survival after major cardiac surgeries has improved & thus post-operative  
276 comorbidities have gained major attention including POCD, which may affect quality of  
277 life of patients after surgery. Incidence of POCD after cardiac surgeries worldwide as  
278 indicated by previous studies range from 5 to 40 percent within first post-operative  
279 week. Preoperative cognitive impairment has been implicated as one of the reason for  
280 development of POCD hence our study focused on comparing the preoperative  
281 cognitive function of the study subjects with their postoperative one.

282 Although the pathogenesis of adverse neurologic events after Valvular heart surgery is  
283 multifactorial, there is growing evidence that patient-related risk factors, such as the  
284 extent of pre-existing cerebrovascular diseases and cognitive impairment have a  
285 greater effect on both short- and long-term neurologic sequelae. The most commonly  
286 used method of assessing patients for cognitive decline after cardiac surgery is  
287 neuropsychological testing. This typically involves administering a battery of tests,  
288 before and after surgery, that examines several cognitive domains, including memory,  
289 attention, language, executive functions, and motor speed. Although such testing allows  
290 for detection of even subtle changes in cognitive performance, it is now increasingly  
291 apparent that the incidence of both short- and long-term cognitive decline after Valvular  
292 heart surgery has been greatly overestimated, owing to the lack of a uniform definition  
293 of what constitutes cognitive decline.

294 In our study emphasis was on accessing the pre-operative cognitive function of the  
295 study subjects using Hindi mini mental scale which is validated as a screening test for  
296 cognitive impairment. Total 110 study subjects were studied, Hindi mini mental scale  
297 was used 24 hours prior to surgery to know the pre-operative cognitive function of the  
298 subject and only those with normal cognitive function were included in the study. Hindi  
299 mini mental scale was applied again post-operatively after 72 hours to find out POCD.  
300 Hindi mini mental scale score of  $-1.5$  Standard deviation from baseline was considered

301 as POCD. Thus, a uniform criterion was used with a valid test to define POCD in study  
302 group.

303 Total 110 cases were studied out of which 8 were above 50 years were comprising  
304 7.27% of study subjects, 21 were between 41 to 50 years of age comprising 19.06% of  
305 the study group. 30(27.27%) were between 31 to 40 years of age. 51 subjects that is  
306 46.36% of study group population was in the range of 30 year Or below., thus major  
307 proportion of subjects were in the range of 30 or below years of age. This age  
308 distribution of study subjects is attributed to incidence of cardiovascular disease and  
309 need for Valvular heart surgery for that population. Age group of 25 to 65 was only  
310 studied as age more than 65 is an independent risk factor affecting the cognitive  
311 function of the patient.

312 Out of 110 study participants 75(68.18%) were Female and 35(31.82%) were male. This  
313 is because of a higher proportion of valvular heart disease in females and a resultant

314 Graph 3 shows the distribution of co-morbidities in study subjects, 36(32.72%) subjects  
315 had isolated hypertension and 38(34.54%) had isolated diabetes while 24 (21.81%) of  
316 them had both diabetes and hypertension. Five (4.54%) study subjects had diabetes  
317 with other co-morbidity like bronchial asthma or hypothyroidism while 7(6.36%) of them  
318 had hypertension with other co-morbidities. Thus, in summary diabetes was the most  
319 commonly associated co-morbidity followed by hypertension and hypertension-diabetes  
320 combined.

321 Subjects having history of stroke or cerebrovascular accidents, psychiatric illness,  
322 documented memory problems like dementia, speech problems were not included in  
323 study to avoid confounding results.

324 Table 2 here depicts the distribution of study subjects as per presence of POCD, 108  
325 (98.18) subjects did not show the post-operative cognitive dysfunction while only two  
326 that is 1.82% showed the POCD.

327 Hindi Mini Mental scale was the test used to define cognitive impairment in our study  
328 which is easy to apply and is in form of a questionnaire which gives a 31-point score  
329 which is again easy to compare. Hindi Mini Mental Scale is a valid test for defining  
330 cognitive function. Battery of five tests was used by Newman et al and mean of each

331 test was calculated, finally scores of all five tests were combined to yield a composite  
332 cognitive index and its mean score was then used to define cognitive function of the  
333 individual. Variation of results is attributed to use of different tests to define subject's  
334 cognition and its impairment.

335 Table 3 shows the gender wise distribution of subjects as per presence of POCD, out of  
336 75 Female patients only one patient developed POCD which is 1.34% of total Female  
337 patients, while 74(98.66%) had normal cognitive function post-operatively. One male  
338 patient out of 35 developed POCD which is 2.86% of total male subjects studied while  
339 rest 34(97.14%) had normal cognitive function post-operatively.

340 Chi square test was applied which yielded a value of 0.310 and p value of 0.5774 as p  
341 value is more than 0.05 this is statistically not significant and thus occurrence of POCD  
342 is not related to gender of the patients.

343 Graph 8 shows the distribution of study subjects as per presence of POCD and Age  
344 Group, of the two patients who developed POCD one is below 45 years of age and  
345 other is having age more than 45 years. Study groups were thus divided above and  
346 below 45 years of age to see whether POCD has any relation to age of the patient.

347 Out of 15 patients of age of above 45 years one patient developed POCD which is  
348 6.66% and 14 patients had normal post-operative cognitive function. In 45 years and  
349 below' age group one patient that is 1.05% showed POCD while 94 had normal post-  
350 operative cognitive function.

351 Chi square test was applied to these observations which yielded a value of 0.223 and p  
352 value of 0.6365, p value is more than 0.05 and hence it is statistically not significant.  
353 Thus, distribution of POCD in study subjects is not related to the age of the patients.

354 Reassessment was scheduled at 72 hours post-operative as it is the period required for  
355 weaning of anesthetic effect and surgery related stress. Also, it is the desired earliest  
356 interval at which any dysfunction if present can be screened with much accuracy. 72  
357 hours post-operative day is the usual time of discharge from CVTS Recovery to ward in  
358 uneventful cases of Valvular Heart Surgery thus an assessment now will help the  
359 patient to seek any medical advice if needed.



360 The two patients who developed POCD had both diabetes mellitus and hypertension  
361 over long duration. Becoz of this comorbidity there are chances of developing  
362 calcification of valve and microemboli.also age of the patient was above 55 years that is  
363 also a independent risk factor for POCD.Cardiopulmonary bypass time intraoperatively  
364 for these patient was more than other patients who didn't develop POCD.

365 Other patient who didn't develop POCD have existing comorbidity of less duration, most  
366 of the patient were of age less than 55 years, less cardiopulmonary bypass time, and  
367 also inspite of use of new generation oxygenator in all patients undergoing valvular  
368 heart surgery using cardiopulmonary bypass circuit, chances of emboli decreases as  
369 compare to past.

370 Results of our study indicate that incidence of POCD is not related to gender of the  
371 study subject, existing comorbidities and their duration. These results are comparable  
372 with those by Newman et al. However, our study did not show a significant association  
373 between POCD and age of the patient, all previous studies including one by Newman et  
374 al have shown that old age is an independent risk factor for developing POCD. It is  
375 related to the inclusion criteria applied in our study as per which age group of 25-65  
376 years was studied, excluding subjects above 65 years of age. Previous studies included  
377 the old age subjects, Newman et al studied a sample of 261 in which age of the patients  
378 was 61+10.6 including a higher number of patients above 65 years of age. Our study  
379 did not show any relation between POCD and number of years of education. Contrary  
380 finding in our study can also be attributed to small sample size studied which is 110  
381 compared with 261 in previous study. Large sample size can provide more comparable  
382 results.

383 To conclude low incidence of POCD in our study is attributed to inclusion criteria for  
384 study subjects as per it only subjects with normal cognition were included in study, Age  
385 group studied was 25 to 65 years and patients with any history of stroke or psychiatric  
386 illness were excluded. Screening test used was Hindi Mini Mental Scale which is a valid  
387 test and POCD defined at -1.5 SD below pre-operative level. All this may be responsible  
388 for a low incidence of POCD 1.82% at 72 hours of surgery.

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## SUMMARY

393 This cross sectional comparative study was conducted to study the POCD in patients  
394 undergoing valular heart surgery using CPB having normal preoperative cognitive  
395 function, conducted in a tertiary care hospital. A total of 110 study subjects fulfilling the  
396 eligibility criteria were included in the study after taking the written informed consent  
397 from the participants. Permission from the institutional ethics committee was obtained.

398 □ 110 subjects with normal preoperative cognition were studied of which two  
399 developed POCD that is incidence of POCD 1.82% on 72 hours post-operatively.

400 □ One male and one female patient developed POCD showing an incidence of  
401 1.34% among Females and 2.86% in males, chi-square test applied showed no  
402 significance between gender of the patient and POCD.

403 □ Forty-five years or less age group had one patient who developed POCD with an  
404 incidence of 1.05% while incidence was 6.6% in above 45 years' age group.  
405 Relationship between age of the study subjects and occurrence of POCD was not  
406 significant.

407 □ Incidence of POCD was 2.38% in study subjects having comorbidities for five  
408 years or less, those who had coexisting diseases for more than 5 years had incidence  
409 of 1.47%. There was no significant relationship between duration of comorbidities and  
410 POCD.

411 □ Both study subjects who developed POCD had 8 years of education and hence  
412 no test of significance was applied.

413 □ Incidence of POCD was found lower that is 1.82% in patients having normal  
414 cognitive function preoperatively.

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## CONCLUSION

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423 POCD is one of the important morbidity in patients undergoing Valvular Heart Surgery; it  
424 can limit neurological function of the subject significantly affecting memory, reasoning,  
425 thought process and mathematical calculations. Neuropsychological tests to determine  
426 preoperative cognitive function should be included in the preoperative examination of  
427 the patients undergoing Valvular Heart Surgery to screen those with impaired cognition,  
428 as they are at an increased risk of developing POCD.

429 As Per our study POCD prevalence is not significant in subjects having normal cognitive  
430 function preoperatively.

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