Glaucoma

Analysis of Cerebrospinal Fluid Pressure Estimation Using Formulae Derived From Clinical Data

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Purpose. To evaluate a frequently used regression model and a new, modified regression model to estimate cerebrospinal fluid pressure (CSFP).

Methods. Datasets from the Beijing iCOP study from Tongren Hospital, Beijing, China, and the Mayo Clinic, Rochester, Minnesota, were tested in this retrospective, case-control study. An often-used regression model derived from the Beijing iCOP dataset, but without radiographic data, was used to predict CSFP by using demographic and physiologic data. A regression model was created using the Mayo Clinic dataset and tested against a validation group. The Mayo Clinic–derived formula was also tested against the Beijing Eye Study population. Intraclass correlation was used to assess predicted versus actual CSFP.

Results. The Beijing-derived regression equation was reported to have an intraclass correlation coefficient (ICC) of 0.71, indicating strong correlation between predicted and actual CSFP in the study population. The Beijing iCOP regression model poorly predicted CSFP in the Mayo Clinic population with an ICC of 0.14. The Mayo Clinic–derived regression model similarly did not predict CSFP in its Mayo Clinic validation group (ICC 0.28 $\pm$ 0.04) nor in the Beijing Eye Study population (ICC 0.06).

Conclusions. Formulae used to predict CSFP derived from clinical data fared poorly against a large retrospective dataset. This may be related to differences in lumbar puncture technique, in the populations tested, or the timing of collection of physiologic variables in the Mayo Clinic dataset. Caution should be used when interpreting results based on formulaic derivation of CSFP.

Keywords: cerebrospinal fluid, cerebrospinal fluid pressure, translaminar pressure, lamina cribrosa, estimation equation

There is growing interest in the role of cerebrospinal fluid pressure (CSFP) in the pathogenesis of glaucoma and other diseases, such as visual impairment/intracranial pressure syndrome.[1] Patients with primary open-angle glaucoma and normal tension glaucoma were found to have lower CSFP compared with patients without glaucoma.[2,3] Those with ocular hypertension were found to have higher CSFP compared with controls.[4,5] It is believed that the difference between the pressure in the eye and the orbital subarachnoid space, or the translaminar pressure differential, is more important than IOP alone. This is in accordance with earlier animal studies that identified the importance of the pressure differential of CSFP and IOP in creating biomechanical stress on the lamina cribrosa.[6,7]

However, the ability to study the association between CSFP and glaucoma is limited due to the invasive nature of determining CSFP. For the purpose of ophthalmologic investigation, performing lumbar punctures to obtain CSFP is impractical. However, development of noninvasive methods would be highly beneficial and is an important goal for many medical specialties. Recently, a regression model to estimate CSFP using radiographic and physiologic parameters, such as optic nerve sheath width as determined by magnetic resonance imaging (MRI), body mass index (BMI), diastolic blood pressure (DBP), and age, was derived from a Chinese dataset in Beijing.[8] This model was reported to have an intraclass correlation coefficient (ICC) of 0.87 when the optic nerve subarachnoid space width was measured at 9 mm and 15 mm posterior to the globe. An equation excluding radiographic measurements that was derived from this set, but not described in the literature, determined an ICC of 0.71, still indicating a strong correlation between predicted and actual CSFP.[9–15] To determine the accuracy or generalizability of this formulaic derivation of CSFP, we examined a large, retrospective dataset compiled from the Mayo Clinic electronic medical records (EMRs).

Methods

The acquisition of data from the Mayo Clinic was approved by the Mayo Clinic Institutional Review Board, and found to be in

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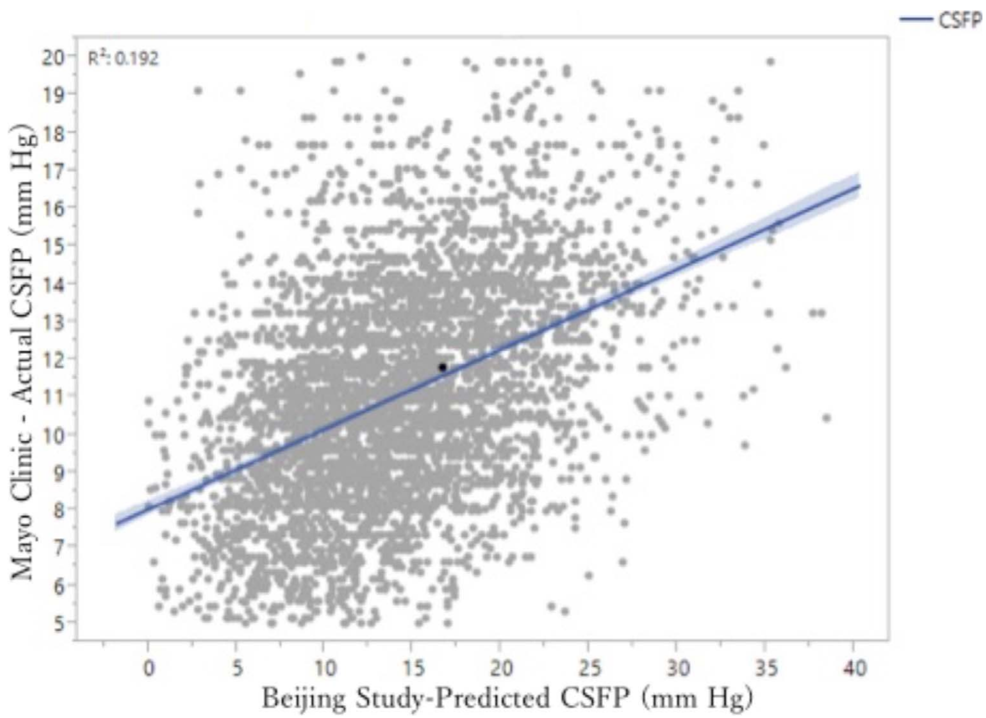

Figure 1. Beijing iCOP formula predicts Mayo Clinic database CSFP. The plot reveals how the Beijing iCOP formula predicts CSFP in the Mayo Clinic database. Estimated pressures less than 0 mm Hg and greater than 40 mm Hg were removed. The r^2 is 0.19.

compliance with the Health Insurance Portability and Accountability Act. We evaluated the predictive accuracy for CSFP by using the modified regression model from Beijing on a large dataset consisting of EMRs of patients who had lumbar punctures performed at the Mayo Clinic between December 1, 1996, and December 31, 2009.[16,17]

At the Mayo Clinic (Rochester, MN, USA), trained teams perform lumbar punctures by using a standardized method. Patients are placed in the lateral decubitus position and the lumbar puncture performed with an 89-mm 20-gauge spinal needle in either the L3-to-L4 or L4-to-L5 intervertebral space. A 550-mm manometer is attached to the stopcock and cerebrospinal fluid (CSF) is allowed to equilibrate. In cases in which standard lumbar puncture was unable to be performed safely, a radiologist performed the lumbar puncture under fluoroscopic guidance. The EMR database does not indicate which method was used for the lumbar puncture.

Physiologic and demographic parameters, such as age, sex, race, ethnicity, height, weight, and blood pressure readings, closest to the time of lumbar puncture within 30 days before or after the opening pressure were extracted. Patients with comorbid medical conditions, head trauma, taking medications known to alter CSFP, undergoing more than one lumbar puncture, or having a neurosurgical procedure were excluded. Patients with CSFP values considered outside of the normal statistical range, <60 or >250 mm H_2O, were excluded from analysis. In total, there were 134 different medications and ICD-9 codes of conditions that could potentially affect CSFP that were used to exclude patients. Of 33,922 patients, 12,118 met all entry criteria. Of 12,118 patient records reviewed, 4314 contained all critical measured variables and met all inclusion and exclusion criteria for entry into the analysis

The Beijing Intracranial and Intraocular Pressure (iCOP) was a prospective observational comparative study including patients who consecutively underwent cranial MRI and a lumbar puncture for the diagnosis and treatment of neurologic diseases.[8] The study was approved by the Medical Ethics Committee of the Beijing Tongren Hospital and met the tenets of the Declaration of Helsinki. Patients with bilateral optic neuritis, optic nerve tumors, ocular or intracranial tumors, visual acuity worse than 20/400, any orbital disease, any cranial surgery, traumatic brain injury, or previous lumbar puncture were excluded from this study. All patients underwent a neurologic and ophthalmologic examination, as well as a cranial and orbital MRI, and lumbar puncture with opening pressure measurement.

Lumbar punctures were performed by the same neurologist in a standardized manner in the lateral decubitus position, with the patient's neck bent in full flexion, and the knees bent in full flexion up to the chest. A standard spinal needle (20-gauge, 90 mm in length) was used, and the opening pressure measured. No patients were sedated during the lumbar punctures. Systolic blood pressure and DBP were measured before the lumbar puncture.[8]

The equation derived from the Beijing iCOP Study used MRI measurements of the optic nerve sheath width. However, all subsequent studies from the Beijing Eye Study 2011 used a different equation, in which the MRI data of the optic nerve sheath width were not used. Therefore, the following equation was used in our study[8]:

$$\mathrm{CSFP(mm\ Hg)} = 0.44 \times \mathrm{BMI(kg/m^2)} + 0.16 \times \mathrm{DBP(mm\ Hg)} - 0.18 \times \mathrm{Age(years)} - 1.91 \quad (1)$$

For derivation of the Mayo Clinic CSFP predictive model, ICC was used to assess predicted versus actual CSFP. All variables available within the Mayo Clinic–derived database were tested, and the variables that were most useful in estimating CSFP were selected. The dataset was thus divided into race-sex-age strata (5-year intervals) and randomly assigned half of each stratum to a training sample. The remaining

Table 1. Results of Model-Fitting in the Training Sample

Parameter	Estimate	SE	*t* Value	Pr > |*t*|
Intercept	9.61986	0.46639	20.63	<0.001
BMI	0.08003	0.00669	11.96	<0.001
Age	−0.04202	0.00355	−11.84	<0.001
Female sex	−0.92634	0.11799	−7.85	<0.001
DBP	0.02621	0.00525	4.99	<0.001

The r^2 for this model was 0.15. The root mean square error was 2.65.

Table 2. Results of Fitting the Same Model in the Validation Sample

Parameter	Estimate	SE	*t* Value	Pr > |*t*|
Intercept	8.09224	0.46066	17.57	<0.001
BMI	0.15511	0.00849	18.25	<0.001
Age	−0.04347	0.00332	−13.08	<0.001
Female sex	−0.71388	0.11218	−6.36	<0.001
DBP	0.01877	0.00503	3.73	<0.001

The r^2 from this model was 0.22. The root mean square error was 2.52.

patients became a validation sample. Using the training sample, a new general linear model was derived by using the same physiologic parameters used by the Beijing Eye Study plus patient gender. Intraclass correlation was used to assess the predictive value of this new model.

The estimation equation derived from the Mayo Clinic dataset was then tested in the Beijing Eye Study population.

Results

The modified Beijing regression equation was reported to have an ICC of 0.71, indicating strong correlation between predicted and actual CSFP in the study population. Using the same Beijing regression equation (Equation 1), we compared results from the predictive model with actual CSFP values in a large Mayo Clinic patient database that has previously been used for association of CSFP and glaucoma.[2,4,16–18] Analysis of the Mayo Clinic dataset showed that the Beijing regression model poorly predicted CSFP in the Mayo Clinic population, with a calculated ICC of 0.14 ± 0.03 (Fig. 1).

Given the poor predictive value of the Beijing regression model for the CSFP in the Mayo Clinic population, a new formula was developed using a Mayo Clinic population that contained 4176 observations, of which 2073 were randomly selected from each age group. This training group ($n = 2073$) was used to develop a Mayo Clinic–based regression model using the following equation:

$$\begin{aligned}\mathrm{CSFP(mm\ Hg)} = {} & 0.08 \times \mathrm{BMI(kg/m^2)} + 0.262 \times \mathrm{DBP(mm\ Hg)} \\ & - 0.042 \times \mathrm{Age(years)} \\ & - 0.962 \times \mathrm{Gender(Female)} + 9.62, \end{aligned} \quad (2)$$

with value for Male = 0, and Female = 1.

The new Mayo Clinic regression formula was validated in the remaining 2103 subjects from the original population of 4176 Mayo Clinic population. Although the Mayo Clinic regression formula fared better than the Beijing regression equation, it still showed poor CSFP predictive value in the validation sample with an ICC of 0.28 ± 0.04. The r^2 value for the training and validation samples was 0.15 and 0.22, respectively. The root mean square error for the training group was 2.65 and for the validation group, 2.52 (Tables 1, 2; Fig. 2). Demographic information for the Mayo Clinic training and

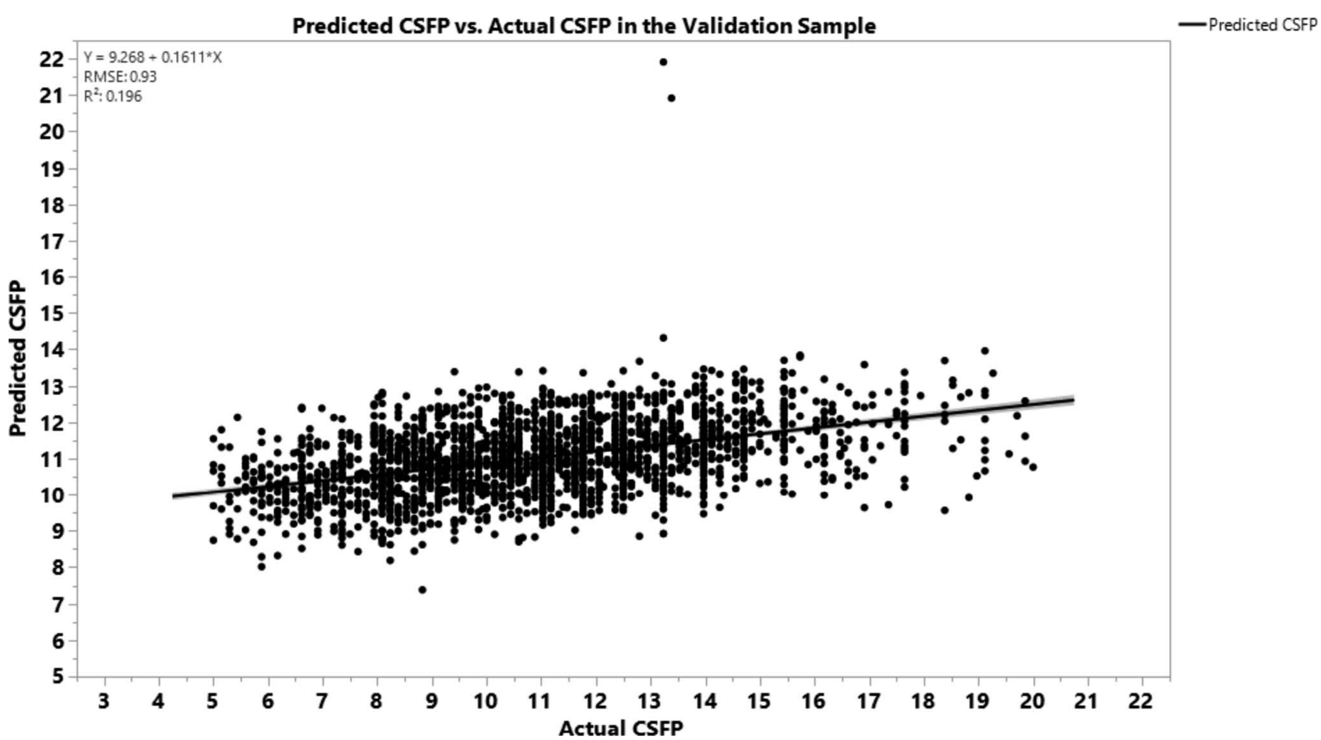

Figure 2. Calculation of validation group CSFP using Mayo Clinic CSFP formula. Low correlation between measured and predicted CSFP using a new regression model derived and tested on the Mayo Clinic dataset. Only measured CSFP values of 5 to 20 mm Hg were included.

TABLE 3. Demographic Information for the Study Subjects in the Beijing iCOP Database With MRI Results and Mayo Clinic Datasets

Variable	Statistic	Beijing, n = 73	Mayo Training, n = 2073	Mayo Validation, n = 2103
Age	Mean (SD)	42.2 (13.4)	53.5 (16.6)	53.5 (16.7)
	Median (Range)	44 (14–70)	55 (10–89)	55 (10–89)
Male sex	n (%)	26 (35.6)	991 (47.8)	1004 (47.7)
Race				
C	n (%)		1702 (82.1)	1716 (81.6)
U	n (%)		371 (17.9)	387 (18.4)
Ethnicity				
H	n (%)		6 (0.3)	14 (0.7)
N	n (%)		511 (24.6)	484 (23.0)
U	n (%)		1553 (74.9)	1603 (76.2)
X	n (%)		3 (0,.1)	1 (0.1)
BMI	Mean (SD)	23.7 (3.2)	27.0 (8.8)	26.8 (6.6)
	Median (Range)	23.7 (16.8–36.1)	26.1 (3.2–246.2)	26.2 (3.9–162.5)
DBP	Mean (SD)	77.3 (8.9)	75.9 (11.2)	76.1 (11.1)
	Median (Range)	80 (60–100)	76 (32–136)	76 (40–1127)

C, Caucasian; H, Hispanic; Max, maximum; Min, minimum; N, Native Hawaiian/Pacific Islander; U, Unknown; X, choose not to disclose.

validation dataset subjects and the Beijing iCOP–derived study subjects are shown in Tables 3 and 4, respectively.

The Mayo Clinic regression formula derived from the Mayo Clinic dataset was finally used to estimate CSFP in the Beijing dataset. The results indicate a very weak correlation, with correlation coefficient of $\beta = 0.34$, ICC of 0.06 (Fig. 3).

DISCUSSION

A regression model to estimate CSFP derived from a Chinese population (Equation 1) did not accurately predict opening pressures in a large, retrospectively sampled population at the Mayo Clinic. Further, an equation derived from this same Mayo

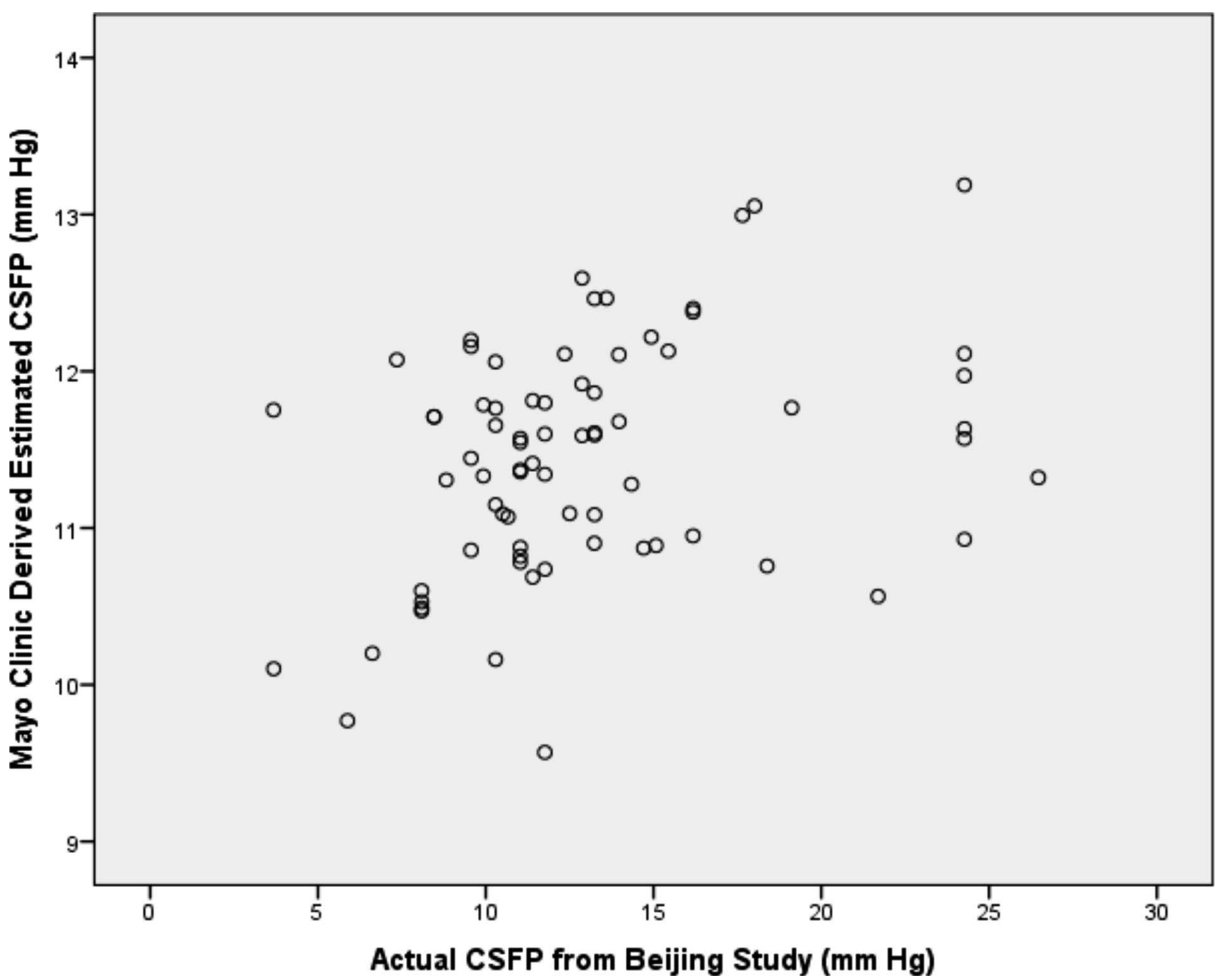

FIGURE 3. The Mayo Clinic–derived CSFP estimation formula tested on the Beijing dataset. The r^2 is 0.30.

TABLE 4. Demographic Information for the Study Subjects From the Beijing iCOP–Derived Database Without MRI Information, and Used in Testing the Mayo Clinic–Derived CSFP Estimation Equation, in Figure 3

	Average	Median	SD	Minimum	Maximum
Age	44.19	45.50	9.8	20	61
BMI	24.06	23.67	3.7	16.82	36.14
Diastolic	79.53	80.00	10.4	60	100
Systolic	119.16	120.0	15.4	90	150

There are 32 subjects (18 male, 14 female). All patients are Asian (Chinese).

Clinic database (Equation 2) poorly predicted the CSFP in both its own population and in the Beijing iCOP patient database. The current study suggests that formulaic estimates of CSF pressure are difficult to generalize and therefore must be used cautiously.

Numerous ophthalmologic studies, mostly from the Beijing Eye Study, have recently been published using an estimated CSFP from a formula derived from clinical data.[9–12,14,15] Because translaminar pressure differential has been recognized as an important risk factor in glaucoma and as a key variable in ocular hypertension, there has been increasing interest in studying CSFP in the context of these ophthalmologic diseases. Due to the invasive nature of testing CSFP, noninvasive measures are desirable. Other techniques that have been explored include IOP measurement,[19] optic nerve sheath width measurement by ultrasonography[20] or MRI,[21,22] and an approach using transcranial Doppler technology.[23] Unfortunately, limitations exist for each of these techniques as well as the technical approach that is being used to estimate CSFP.

In the current study, CSFP and medical data obtained from the Mayo Clinic EMR are retrospective in nature with all of the limitations associated with this approach including diagnostic coding inaccuracy and asynchronous measurements for blood pressure and other physiologic parameters, including lumbar puncture data. These and other aspects of data collected from an EMR may affect interpretation of the interrelationship between blood pressure and CSFP. It is important to note that the formula used in the Beijing Eye Study was not explicitly included in the study by Xie et al.,[8] but rather derived from its dataset, and not described in the article. Our current study did not test the validity or generalizability of the Beijing iCOP formula that used MRI data of the optic nerve subarachnoid space width.

Other possible limitations of our study also should be mentioned. First, in addition to the factors related to the retrospective nature of the present study, the discrepancy between the Mayo Clinic–derived formula and the regression equation used by the Beijing Eye Study may reflect ethnicity-related differences between the two populations, differences in lumbar puncture technique, or unknown medical or environmental factors. Second, blood pressure in our sample was at times measured several days from the determination of the lumbar CSFP. Third, blood pressure–lowering medication might have had a different effect on blood pressure and CSFP. Fourth, regardless of the accuracy of noninvasive, calculated CSFP estimates, a major issue remains: none of these approaches, even if accurate, measure the CSFP of the perioptic subarachnoid space, which is the critical measurement contributing to the translaminar pressure differential. Anatomic and physiologic studies have suggested that the orbital subarachnoid space is compartmentalized, and that clinically measured CSFP may not in fact translate to the perioptic subarachnoid CSFP.[24] This would imply that the measurements here have even less certain clinical significance. Ultimately, the only way to most accurately measure CSFP remains lumbar puncture.

In conclusion, formulae used to predict CSFP derived from clinical data fared poorly against a large retrospective dataset. Caution should therefore be used when interpreting results derived using formulaic derivations of CSFP.

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References

1. Alexander DJ, Gibson CR, Hamilton DR, et al. Evidence Report: Risk of Spaceflight-Induced Intracranial Hypertension and Vision Alterations. Contract No.: 1.0. Houston TX: Lyndon B. Johnson Space Administration; 2012.
2. Berdahl JP, Allingham RR, Johnson DH. Cerebrospinal fluid pressure is decreased in primary open-angle glaucoma. *Ophthalmology*. 2008;115:763–768.
3. Ren R, Jonas JB, Tian G, et al. Cerebrospinal fluid pressure in glaucoma: a prospective study. *Ophthalmology*. 2010;117:259–266.
4. Berdahl JP, Fautsch MP, Stinnett SS, Allingham RR. Intracranial pressure in primary open angle glaucoma, normal tension glaucoma, and ocular hypertension: a case-control study. *Invest Ophthalmol Vis Sci*. 2008;49:5412–5418.
5. Ren R, Zhang X, Wang N, Li B, Tian G, Jonas JB. Cerebrospinal fluid pressure in ocular hypertension. *Acta Ophthalmol*. 2011;89:e142–e148.
6. Morgan WH, Chauhan BC, Yu DY, Cringle SJ, Alder VA, House PH. Optic disc movement with variations in intraocular and cerebrospinal fluid pressure. *Invest Ophthalmol Vis Sci*. 2002;43:3236–3242.
7. Morgan WH, Yu DY, Cooper RL, Alder VA, Cringle SJ, Constable IJ. The influence of cerebrospinal fluid pressure on the lamina cribrosa tissue pressure gradient. *Invest Ophthalmol Vis Sci*. 1995;36:1163–1172.
8. Xie X, Zhang X, Fu J, et al. Noninvasive intracranial pressure estimation by orbital subarachnoid space measurement: the Beijing Intracranial and Intraocular Pressure (iCOP) study. *Crit Care*. 2013;17:R162.
9. Jonas JB, Wang N, Wang S, et al. Retinal vessel diameter and estimated cerebrospinal fluid pressure in arterial hypertension: the Beijing Eye Study. *Am J Hypertens*. 2014;27:1170–1178.
10. Jonas JB, Wang N, Wang YX, et al. Body height, estimated cerebrospinal fluid pressure and open-angle glaucoma. The Beijing Eye Study 2011. *PLoS One*. 2014;9:e86678.
11. Jonas JB, Wang N, Wang YX, You QS, Yang D, Xu L. Ocular hypertension: general characteristics and estimated cerebrospinal fluid pressure. The Beijing Eye Study 2011. *PLoS One*. 2014;9:e100533.
12. Jonas JB, Wang N, Xu J, et al. Diabetic retinopathy and estimated cerebrospinal fluid pressure. The Beijing Eye Study 2011. *PLoS One*. 2014;9:e96273.

13. Wang YX, Jonas JB, Wang N, et al. Intraocular pressure and estimated cerebrospinal fluid pressure. The Beijing Eye Study 2011. *PLoS One*. 2014;9:e104267.
14. Jonas JB, Wang N, Wang YX, et al. Incident retinal vein occlusions and estimated cerebrospinal fluid pressure. The Beijing Eye Study. *Acta Ophthalmol*. 2015;93:e522–e526.
15. Jonas JB, Wang NL, Wang YX, et al. Estimated trans-lamina cribrosa pressure difference versus intraocular pressure as biomarker for open-angle glaucoma. The Beijing Eye Study 2011. *Acta Ophthalmol*. 2015;93:e7–e13.
16. Berdahl JP, Fleischman D, Zaydlarova J, Stinnett SS, Allingham RR, Fautsch MP. Body mass index has a linear relationship with cerebrospinal fluid pressure. *Invest Ophthalmol Vis Sci*. 2012; 53:1422–1427.
17. Fleischman D, Berdahl JP, Zaydlarova J, Stinnett SS, Fautsch MP, Allingham RR. Cerebrospinal fluid pressure decreases with older age. *PLoS One*. 2012;7:e52664.
18. Fleischman D, Berdahl J, Stinnett SS, Fautsch MP, Allingham RR. Cerebrospinal fluid pressure trends in diseases associated with primary open-angle glaucoma. *Acta Ophthalmol*. 2015; 93:e234–e236.
19. Sajjadi SA, Harirchian MH, Sheikhbahaei N, Mohebbi MR, Malekmadani MH, Saberi H. The relation between intracranial and intraocular pressures: study of 50 patients. *Ann Neurol*. 2006;59:867–870.
20. Rajajee V, Vanaman M, Fletcher JJ, Jacobs TL. Optic nerve ultrasound for the detection of raised intracranial pressure. *Neurocrit Care*. 2011;15:506–515.
21. Rohr A, Jensen U, Riedel C, et al. MR imaging of the optic nerve sheath in patients with craniospinal hypotension. *AJNR Am J Neuroradiol*. 2010;31:1752–1757.
22. Rohr AC, Riedel C, Fruehauf MC, et al. MR imaging findings in patients with secondary intracranial hypertension. *AJNR Am J Neuroradiol*. 2011;32:1021–1029.
23. Siaudvytyte L, Januleviciene I, Ragauskas A, Bartusis L, Siesky B, Harris A. Update in intracranial pressure evaluation methods and translaminar pressure gradient role in glaucoma. *Acta Ophthalmol*. 2015;93:9–15.
24. Killer HE, Miller NR, Flammer J, et al. Cerebrospinal fluid exchange in the optic nerve in normal-tension glaucoma. *Br J Ophthalmol*. 2012;96:544–548.

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