**Supplemental Table 22. Strength of evidence for possible risk factors for delirium**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
| Variables | Positive association | Negative association | No association | Level of evidence |
| **Predisposing variables:** |  |  |  |  |
| *Patient characteristics:* |  |  |  |  |
| Age | **Abelha 2012 [1]****Angles 2008 [2]****Pandharipande 2006 [3]****Pandharipande 2009 [4]****Serafim 2012 [5]****Shehabi 2013 [6]****Veiga 2012 [7]****Yoshitaka 2013 [8]****Schreiber 2014 [9]***Bryczkowski 2014 [10]**Colombo 2012 [11]**Shi 2010 [12]**Simons 2014[13]**Zaal 2012 [14]**Van Rompaey 2012 [15]**Leite 2014 [16]* |  | **Ely 2007 [17]****Kamdar 2015 [18]****Morandi 2013 [19]****Zhang 2014 [20]***Hsieh 2014*  **[21]***Lin 2015 [22]**Skrobik 2013[23]**Mehta 2015 [24]* | Strong |
| Gender |  |  | **Schreiber 2014 [25]****Shehabi 2013 [6]****Zhang 2014 [20]***Simons 2014 [13]**Skrobik 2013[23]**Zaal 2012* *[14]**Leite 2014 [16]* | Strong |
| Ethnicity |  |  | **Kamdar 2015 [18]** | Inconclusive |
| Body Mass Index |  |  | *Skrobik 2013 [23]* | Inconclusive |
| Sensory impairment |  |  | *Lin 2015[22]* | Inconclusive |
| Non-English language | *Hsieh 2014 [21]* |  |  | Inconclusive |
| Living alone |  |  | **Zhang 2014 [20]** | Inconclusive |
| Home sleep quality |  |  | **Kamdar 2015 [18]** | Inconclusive |
| ASA score | **Veiga 2012 [7]****Whitlock 2014 [26]** |  |  | Strong |
| Prehospital statin use |  | *Lin 2015[22]* |  | Inconclusive |
| Nicotine use | *Van Rompaey 2012* [15] |  | **Zhang 2014 [20]***Dubois 2001* [27]*Mehta 2015 [24]**Skrobik 2013 [23]* | Moderate |
| Alcohol use | **Ouimet 2007 [28]***van Rompaey 2009* [29]*Heymann 2007* [30]*Hsieh 2014 [21]* |  | **Zhang 2014 [20]***Mehta 2015 [24]**Skrobik 2013 [23]* | Inconclusive |
| Recreational drug use |  |  | *Hsieh 2014 [21]* | Inconclusive |
| *Chronic pathology:* |  |  |  |  |
| Vascular system: |  |  |  |  |
| Cardiac disease | **Abelha 2012 [1]** |  | *Mehta 2015 [24]* | Inconclusive |
| Hypertension | **Ouimet 2007 [28]***Dubois 2001* [27] |  |  | Moderate |
| Hypotension | *Aldemir 2001* [31] |  |  | Inconclusive |
| Respiratory system |  |  |  |  |
| Respiratory disease | *Aldemir 2001* [31] |  | **Ely 2007 [17]***Lin 2015 [22]* | Moderate |
| Nervous system |  |  |  |  |
| Stroke | *Limpawattana 2014 [32]**Shi 2010 [12]* |  | *Lin 2015 [22]* | Inconclusive |
| Dementia | **McNicoll 2003 [33]****Pisani 2007 [34]***Hsieh 2014 [21]**Pisani 2009 [35]**van Rompaey 2009* [29] |  | **Pandharipande 2009 [4]** | Strong |
| Other Neurologic condition | *Leite 2014 [16]* |  | *Mehta 2015 [24]* | Inconclusive |
| Other: |  |  |  |  |
| Diabetes Mellitus |  |  | **Lin 2008** [36] | Inconclusive |
| Liver dysfunction |  |  | *Skrobik 2013 [23]* | Inconclusive |
| Renal dysfunction |  |  | *Skrobik 2013 [23]* | Inconclusive |
| Dialysis or CVVH  |  |  | **Shehabi 2013 [6]***Mehta 2015 [24]* | Moderate |
| **Precipitating variables:** |  |  |  |  |
| *Acute illness:* |  |  |  |  |
| Emergency surgery or trauma | **Abelha 2012 [1]****Serafim 2012 [37]****Veiga 2012 [7]** |  |  | Strong |
| Delirium previous day (e.g. mental status <24h) | **Agarwal 2010 [38]****Pandharipande 2009 [4]** |  |  | Strong |
| Previous coma | **Agarwal 2010 [38]****Ely 2007 [17]****Ouimet 2007 [28]** |  | *Mehta 2015 [24]* | Strong |
| Fever | *Aldemir 2001* [31] |  |  | Inconclusive |
| Sepsis | **Lin 2008 [36]***Aldemir 2001* [31]*Simons 2014 [13]* |  | **Schreiber 2014 [25]**Shehabi 2013 [6]*Hsieh 2014 [21]* | Inconclusive |
| Pneumonia | *Heymann 2007* [30] |  |  | Inconclusive |
| Poly(trauma) | **Serafim 2012 [5]***Heymann 2007* [30]*Simons 2014 [13]* | *Bryczkowski 2014 [10]* |  | Moderate |
| TBI  |  |  | *Bryczkowski 2014 [10]* | Inconclusive |
| *Medication:* |  |  |  |  |
| Benzodiazepine  | **Agarwal 2010 [38]****Pisani 2007 [39]****Serafim 2012 [5]****Seymour 2012 [40]****Pandharipande 2006** **Pandharipande 2008** *Hsieh 2014 [21]**Pisani 2009 [41]**Skrobik 2013 [23]* | *Mehta 2015 [24]**Svenningsen 2013* [42] | **Schreiber 2014 [9]****Ely 2007 [17]****Pandharipande 2008** [43]**Pandharipande 2009 [4]** **Pandharipande 2006 [3]** *Bryczkowski 2014 [10]* | Strong |
| Opioid  | *Dubois 2001* [27]*Svenningsen 2013* [42] | **Agarwal 2010** [38]**Pandharipande 2008** [43] | **Schreiber 2014 [9]****Pandharipande 2006 [3]****Pandharipande 2008** [43]**Pandharipande 2009 [4]***Skrobik 2013 [23]**Hsieh 2014 [21]**Mehta 2015 [24]* | Strong |
| Vasopressor |  |  | **Shehabi 2013** [6] | Inconclusive |
| Steroid | **Schreiber 2014 [25]** |  | **Schreiber 2014 [25]***Hsieh 2014 [21]*Wolters 2015 [44] | Inconclusive |
| (Analgo)sedation  | *Colombo 2012 [11]**Simons 2014 [13]* |  | **Shehabi 2013** [6]*Bryczkowski 2014 [10]* | Inconclusive |
| Psychoactive medication | *van Rompaey 2009* [29]*Mehta 2015 [24]**Pisani 2009 [45]* |  | **Pandharipande 2006 [3]** | Moderate |
| Anticholinergic drugs |  |  | **Pandharipande 2006 [3]** | Inconclusive |
| H2 blokker  |  |  | **Pandharipande 2008** [43] | Inconclusive |
| Propofol | *Hsieh 2014 [21]* |  | **Pandharipande 2006 [3]**Seymour 2012 [40]*Svenningsen 2013* [42] | Moderate |
| Paired sedation and ventilator weaning protocol vs sedation per usual care plus daily ventilator weaning |  |  | **Girard 2008 [46]** | Inconclusive |
| Received sedative infusion while not mechanically ventilated |  |  | **Kamdar 2015 [18]** | Inconclusive |
| Received sedative infusion while mechanically ventilated | **Kamdar 2015 [18]** |  |  | Inconclusive |
| Anesthetics |  |  | **Pandharipande 2008** [43] | Inconclusive |
| Epidural analgesia | *Dubois 2001* [47] |  | **Yoshitaka 2013 [8]** | Inconclusive |
| Other medication: |  |  |  |  |
| Emergency admission |  |  | *Zaal 2012* [14] | Inconclusive |
| Melatonin |  | **Yoshitaka 2013 [8]** |  | Inconclusive |
| Uses pharmacological sleep aids at home |  |  | **Kamdar 2015 [18]** | Inconclusive |
| ***Blood values /enzymes/proteins:*** |  |  |  |  |
| Hyperglycemia | *Heymann 2007* [30] |  |  | Inconclusive |
| Anemia | *Aldemir 2001 [31]*  |  |  | Inconclusive |
| Bilirubine  | *Dubois 2001* [27]*Aldemir 2001* *[31]* |  |  | Inconclusive |
| Hypoalbuminemia | **Lin 2008 [36]** |  |  | Inconclusive |
| Hypocalcemia | *Aldemir 2001* *[31]* |  |  | Inconclusive |
| Hyponatremia | *Aldemir 2001* *[31]* |  |  | Inconclusive |
| Creatinine > 2mg/dL | **Pisani 2007 [39]** |  |  | Inconclusive |
| Arterial pH <7.35 | **Pisani 2007 [39]** |  |  | Inconclusive |
| Reactive hyperemia index |  |  |  | Inconclusive |
| Elevated serum urea nitrogen | *Aldemir 2001* *[31]* |  |  | Inconclusive |
| Elevated hepatic enzymes | *Aldemir 2001* *[31]* |  |  | Inconclusive |
| Hyperamylasemia | *Aldemir 2001* *[31]* |  |  | Inconclusive |
| Metabolic acidosis | *Aldemir 2001* *[31]* |  |  | Inconclusive |
| APOE4 present | **Ely 2007 [17]** |  |  | Inconclusive |
| MMP-9 |  | **Girard 2012**  **[48]** |  | Inconclusive |
| sTNFR1 | **Girard 2012 [48]** |  |  | Inconclusive |
| Protein C |  | **Girard 2012**  **[48]** |  | Inconclusive |
| IGF-1 |  |  | **Morandi 2011** [49] | Inconclusive |
| 25-OHD |  |  | **Morandi 2013 [50]** | Inconclusive |
| Serum cortisol  | *Shi 2010 [12]* |  |  | Inconclusive |
| Tryptophan/LNAA ratio | **Pandharipande 2009 [4]** |  |  | Inconclusive |
| Tyrosine/LNAA ratio | **Pandharipande 2009 [4]** |  |  | Inconclusive |
| Phenylalanine/LNAA ratio |  |  | **Pandharipande 2009 [4]** | Inconclusive |
| Ventilation: |  |  |  |  |
| Mechanical ventilation | **Guillamondegui 2011 [51]***Bryczkowski 2014 [10]**van Rompaey 2009* [29]*Hsieh 2014 [21]* |  | **Kamdar 2015 [18]****Zhang 2014 [20]****Yoshitaka 2013 [8]***Lin 2015[22]**Limpawattana 2016 [32]* | Strong |
| Scores: |  |  |  |  |
| SOFA  | **Angles 2008 [2]***Heymann 2007* [30]*Zaal 2012* [14]*Van Rompaey 2012 [15]**Leite 2014* [16] |  | **Schreiber 2014 [25]** | Inconclusive |
| GCS  |  |  | **Angles 2008 [2]***Bryczkowski 2014 [10]* | Moderate |
| APACHE  | **Morandi 2013 [50]****Ouimet 2007 [28]****Pandharipande 2006 [3]****Pandharipande 2009 [4]****Schreiber 2014 [9]****Yoshitaka 2013 [8]****Zhang 2014 [20]****Serafim 2012 [5]***Heymann 2007* [30]*Pisani 2009 [35]**Shi 2010 [12]**Simons 2014 [13]**Hsieh 2014 [21]**Leite 2014 [16]* | *Zaal 2012* [14] | **Ely 2007[17]****Shehabi 2013** [6]*Lin 2015 [22]**Skrobik 2013 [23]**Mehta 2015 [24]* | Strong |
| Charlson Comorbidity Index |  |  | *Hsieh 2014[21]* | Inconclusive |
| Charlson Comorbidity Index ≥1 |  |  | *Zaal 2012* [14] | Inconclusive |
| Charlson Comorbidity Index ≥3 | *Zaal 2012* [14] |  |  | Inconclusive |
| RASS | *Svenningsen 2013* [42] |  | *Lin 2015[22]* | Inconclusive |
| Pain (assessed by NRS) |  | **Ouimet 2007** [28] |  | Inconclusive |
| Total quality on RCSQ |  |  | **Kamdar 2015 [18]** | Inconclusive |
| **Admission** |  |  |  |  |
| Medical admission | *van Rompaey 2009* [29] |  | **Shehabi 2013** [6]*Zaal 2012* [29]*Simons 2014 [13]* | Moderate |
| Cardiac admission |  |  | **Shehabi 2013** [6] | Inconclusive |
| Surgical Admission | *Zaal 2012* [29] |  | **Shehabi 2013** [6] | Inconclusive |
| Neurological Admission | *Zaal 2012* [14]*Simons 2014 [13]* |  |  | Moderate |
| Season admission |  |  | *Simons 2014 [13]* | Inconclusive |
| During hospital stay: |  |  |  |  |
| Bed change > 3 | *Limpawattana 2016[32]* |  |  | Inconclusive |
| Physical restraints | *Limpawattana 2016 [32]**Mehta 2015* |  | **Zhang 2014 [20]** | Inconclusive |
| Use of bladder catheter |  |  | *Limpawattana 2016 [32]* | Inconclusive |
| Length of stay |  |  | *Lin 2015 [22]* | Inconclusive |
| Other: |  |  |  |  |
| Duration of dehydration | *Lin 2015 [22]* |  |  | Inconclusive |
| Duration of surgery |  |  | **Yoshitaka 2013 [8]** | Inconclusive |
| Anxiety | **Ouimet 2007 [52]**  |  |  | Inconclusive |
| Hospital LOS before ICU |  |  | **Zhang 2014 [20]** | Inconclusive |
| Transfusion (e.g. packed RBC’s, Fresh Frozen Plasma) | **Angles 2008 [2]****Whitlock 2014 [26]****Veiga 2012 [7]** |  |  | Strong |

High quality studies are shown in **bold**, investigations of acceptable quality in *italics*, and low quality studies are underlined. APACHE=Acute Physiology and Chronic Health Evaluation, APOE=apolioprotein E, ASA score= American Society of Anesthesiology score, CVVH=continuous veno-venous hemofiltration¸ GCS=Glasgow Coma Scale, ICU=Intensive Care Unit, IGF-1=Insuline-like growth factor-1, LNAA=Large Neutral Amino Acids, LOS=length of stay, MMP-9=Matrix Metalloproteinase-9, NRS=Numeric Rating Scale, RASS= Richmond Agitation-Sedation Scale, RBC=red blood cells, RCSQ= Richards–Campbell Sleep Questionnaire, SOFA= Sequential Organ Failure Assessment, sTNFR1=soluble Tumor Necrosis Factor Receptor-1, TBI=Traumatic Brain Injury, 25-OHD=25-hydroxyvitamin D.

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